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# DEPARTMENTS OF LABOR, AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1969

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## HEARINGS

BEFORE A

## SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETIETH CONGRESS

SECOND SESSION

SUBCOMMITTEE ON DEPARTMENTS OF LABOR, AND HEALTH, EDUCATION, AND WELFARE AND RELATED AGENCIES

DANIEL J. FLOOD, Pennsylvania, *Chairman*

WILLIAM H. NATCHER, Kentucky
NEAL SMITH, Iowa
W. R. HULL, Jr., Missouri
BOB CASEY, Texas
MELVIN R. LAIRD, Wisconsin
ROBERT H. MICHEL, Illinois
GARNER E. SHRIVER, Kansas

ROBERT M. MOYER, *Staff Assistant to the Subcommittee*

## PART 5

## NATIONAL INSTITUTES OF HEALTH

Printed for the use of the Committee on Appropriations

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## NATIONAL INSTITUTES OF HEALTH



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U.S. GOVERNMENT PRINTING OFFICE

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# DEPARTMENTS OF LABOR, AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1969

THURSDAY, MARCH 14, 1968.

## NATIONAL INSTITUTES OF HEALTH

### WITNESSES

DR. JAMES A. SHANNON, DIRECTOR
DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NATIONAL INSTITUTES OF HEALTH
DR. JOHN F. SHERMAN, ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAMS, NATIONAL INSTITUTES OF HEALTH
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LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. MILO D. LEAVITT, JR., DIRECTOR, OFFICE OF PROGRAM PLANNING, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES F. KELLY, ASSISTANT SECRETARY, COMPTROLLER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We will now open our hearings on the National Institutes of Health. The presentation will be made by the distinguished Director, Dr. James A. Shannon.

### TRIBUTE TO DR. SHANNON

Speaking for myself and I am sure for this subcommittee, and I believe for the Congress and the country, we are acutely distressed to realize that this may be your last appearance before us in your capacity as Director of the National Institutes of Health. This grieves us deeply.

Finding a successor for you will be no easy job. I am sure because of the size of your shoes they are going to be very, very difficult, if not impossible, to fill. It would be my hope that you would go on in your present capacity. I personally, as chairman of this subcommittee have tried to prevail upon you to change your mind about retirement and I don't know whether I did or not.

For the last 13 years or more at NIH, during the development of

these institutes you have performed something in the nature of minor miracles in Government administration. Your outstanding service and leadership has attracted these extraordinary and brilliant people who have made the NIH an institution without peer.

I feel that the Congress of the United States, for your service in this field should pass a resolution striking a medal to be awarded to you before you retire. I have mentioned to some of the members that your name should join the list of distinguished contributors to the service of our country in this regard. I don't like to embarrass you by saying anything further, but it would occur to me Mr. Laird would want to comment. He has had much more experience with this subcommittee and with your performance than I have.

Mr. LAIRD. Thank you very much, Mr. Chairman. I have had the opportunity of knowing Dr. Shannon for a good many years. I started serving on this subcommittee in 1953, and he became Director of the National Institutes of Health in 1955 and has served in that capacity for the past 13 years. Prior to that time he had been with the National Heart Institute since 1949. Then, he was Associate Director of the National Institutes of Health for about 3 years. He proceeded to take over full responsibilities for the most rapidly growing agency in the Federal Government during the period 1955 until 1964; and, as everyone knows, he is still the distinguished Director of the NIH. No agency has had a comparable rapid growth without tremendous administrative problems, and NIH has not had these great problems. The country has been well served that this agency did not experience these problems.

The National Institutes of Health has served various purposes, the most important of which was to seek through research the cure and causes of disease. But the NIH has also made possible the medical educational program we have in the United States through the very understanding administration of Dr. Shannon and the Directors of the various institutes and the Public Health Service. They were willing to make a broad interpretation of the authorizing legislation in order to make possible the continued expansion in medical education. Traineeship programs, fellowship programs, and manpower programs have been almost as important as the research program. Many people I think fail to realize that it was through a liberal intrepretation of the word "research" that this was possible. But the United States would be in pretty bad shape today if it were not for the National Institutes of Health. I am proud that the United States is the leader in the world today in the field of medical research. I would rather be ahead in this very important human area than be ahead on the moon. I am more interested in the millions of people that live here on earth than how we are going to get a few people on the moon.

I think that Dr. Shannon through the work he has done and the leadership he has given this agency is deserving of the highest praise, not only of the Congress, but of every citizen in the United States. We hate to see him leave. I hope this is not his last appearance before the committee, but as one member of the subcommittee, I express my deep appreciation for the fine working relationship we have had. I would be remiss if I did not say that the former chairman of this committee, who broke me in, in the area of health, education, and welfare, John Fogarty, had the highest respect and admiration for Dr. Shannon. It was a fine relationship, both official and personal, that he

had with the Director of the National Institutes of Health, Dr. Shannon.

Mr. FLOOD. Thank you, Mr. Laird.

Dr. SHANNON. Mr. Chairman, may I just say how much I appreciate your comments and those of Mr. Laird, but you leave me a little choked up. Thank you.

Mr. LAIRD. Mr. Chairman, there is one further remark that I would like to make.

TRIBUTE TO JAMES F. KELLY

Speaking of tributes to people in the Department of Health, Education, and Welfare, I notice that as the presentation of this budget for the NIH starts this afternoon, we have in the room with us the Assistant Secretary and Comptroller of Health, Education, and Welfare, Jim Kelly. He has already achieved great distinction in many ways as an administrator in the Department of Health, Education, and Welfare, and I have just been informed that he is to be the recipient of the National Civil Service League Award of 1968. This will be awarded to him in April. I think we should take note of the fact that the Assistant Secretary and Comptroller of the Department is here, and I would like to congratulate him on this fine distinction of receiving the National Civil Service League Award of 1968.

Mr. KELLY. Thank you.

Mr. FLOOD. I certainly hasten to embrace those remarks and point out that it couldn't happen to a more devoted or experienced or proper Government official.

FISCAL RESTRAINT REFLECTED IN 1969 BUDGET

Dr. Shannon, now that we have praised you so highly, we find your budget has come down on the conservative side. The increase in the budget of the National Institutes of Health has been dramatic under your leadership in the last 10 years. But this year, except for the Institute of Child Health and Human Development, not one of the institutes has as much as a 5-percent increase; not one. Why were they held down so tight? These increases of 2, 3, and 4 percent won't even cover the increased costs of doing business, will they?

Dr. SHANNON. Mr. Flood, I would say that is correct. I would emphasize, as I will in my statement, that the budget before you does not represent scientific professional opportunities but rather the fiscal restraint within which we operate. I think that within those restraints it is a well-balanced budget. In certain of the appropriations they do make it hard to go forward. However, within the restraints brought upon the Federal budget by trouble in the cities, by balance-of-payment problems, by military activities overseas, and within our dollar ceiling, we present to you a balanced budget. Would that it were possible that these constraints did not exist. We were asked to present to you, within them, our best judgment of how the funds can best be distributed to satisfy our needs. This is what we have done.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. I see you have before us your curriculum vitae. That must go back to Holy Cross, doesn't it?

Dr. SHANNON. That would be at the top.

Mr. FLOOD. Everything you do is impressive, and so is your biographical sketch. It is one of which anyone should be proud. We will insert it at this point in the record.

(The biographical sketch follows:)

CURRICULUM VITAE

Name: James Augustine Shannon.
Date and place of birth: August 9, 1904, Hollis, New York City, N.Y.
Education:
A.B., College of the Holy Cross, 1925.
M.D., New York University, 1929.
Ph. D., New York University, 1935.
Professional positions held:
1929–31: Intern, Bellevue Hospital, New York City.
1931–32: Clinical assistant visiting physician, Third (NYU) Medical Division, Bellevue Hospital, New York City.
1931–32: Assistant in physiology, New York University College of Medicine, New York City.
1932–35: Instructor in physiology, New York University College of Medicine, New York City.
1935–41: Assistant professor of physiology, New York University College of Medicine, New York City.
1936: Guest investigator, Physiological Laboratory, Cambridge University, England.
1938–42: Assistant visiting physician, Third (NYU) Medical Division, Bellevue Hospital, New York City.
1941–42: Assistant professor of medicine, New York University College of Medicine, New York City.
1941–46: Director, Research Service, Third (NYU) Medical Division, Goldwater Memorial Hospital, New York City.
1942–46: Associate professor of medicine, New York University College of Medicine, New York City.
1944: Associate visiting neuropsychiatrist, Third Psychiatric Service (Third Medical Division), Bellevue Hospital, New York City.
1944–45: Acting director, Third (NYU) Medical Division, Goldwater Memorial Hospital, New York City.
1946–47: Chairman, Malaria Study Section, National Institutes of Health, Bethesda, Md.
1946–49: Director, Squibb Institute for Medical Research, New Brunswick, N.J.
1946–49: Special consultant to Surgeon General, U.S. Public Health Service.
1946–49: Member, Study Section, National Institutes of Health, Bethesda, Md.
1949–52: Associate Director (in charge of research), National Heart Institute, National Institutes of Health, Bethesda, Md. (Appointed to Commissioned Corps, Public Health Service, 1949.)
1952–55: Associate director (in charge of intramural affairs), National Institutes of Health, Bethesda, Md.
1955 to date: Director, National Institutes of Health, Bethesda, Md.
Activities during the war:
1941–46:
Malaria Conference, National Research Council.
Chairman, Atabrine Conference, National Research Council.
Member, Subcommittee for Coordination of Malarial Studies, National Research Council.
Member, Board for Coordination of Malarial Studies.
Chairman, Panel on Clinical Testing of Antimalarials.
Consultant to Secretary of War.
1948: Medal for Merit (Presidential).
Scientific societies:
American Physiological Society.
American Public Health Association; Governing Council 1959–62; Fellow 1956.

American Society for Pharmacology & Experimental Therapeutics.
American Society for Clinical Investigation.
Society for Experimental Biology & Medicine.
American Association for the Advancement of Science.
Association of American Physicians.
Washington Academy of Sciences.
Harvey Society.
Alpha Omega Alpha.
Sigma Xi.
American Academy of Arts & Sciences.
American Philosophical Society.

Professional activities:

1951–56: Member, Subcommittee on Malaria of the Committee on Medicine, National Research Council.
1952–56: Member, Subcommittee on Shock of the Committee on Surgery, National Research Council.
1953–56: Chairman, Malaria Panel, National Research Council.
1953–54: Member, Panel on Allocation of Gamma Globulin, National Research Council.
1953 to date: Member, Division of Medical Sciences, National Research Council.
1953–60: Member, Executive Committee, Division of Medical Sciences, National Research Council.
1955 to date: Public Health Service representative, Division of Medical Sciences, National Research Council.
1955–62: Member, U.S. National Committee for the International Union of Physiological Sciences.
1954 to date: Member, board of directors, Gorgas Memorial Institute of Tropical and Preventive Medicine.
1956–66: Member, Expert Advisory Panel on Malaria, World Health Organization.
1959–63: Member, Advisory Committee on Medical Research, World Health Organization.
1959–64 Member, Standing Committee, Federal Council for Science and Technology.
1959–65: Consultant, President's Science Advisory Committee.
1962–66: Member, Advisory Committee on Medical Research, Pan American Health Organization.
1963 to date: Consultant to Advisory Committee on Research to the Agency for International Development.
1965 to date: Department of Health, Education, and Welfare, alternate representative to Federal Council for Science and Technology.
1965 to date: U.S. Delegate to the United States-Japan Cooperative Medical Science Committee.
1967–69: Member, President's Committee on the National Medal of Science.
1967 to date: Member, Board on Medicine, National Academy of Sciences.

*Honorary degrees:*

1952: Doctor of science, College of the Holy Cross.
1957: Doctor of laws, Notre Dame.
1958: Doctor of science, Duke University.
1958: Doctor of science, Providence College.
1959: Doctor of science, Loyola University, Chicago.
1960: Doctor of science, Catholic University.
1960: Doctor of science, University of West Virginia.
1962: Doctor of humane letters, Albert Einstein College of Medicine, Yeshiva University.
1964: Doctor of medicine, Catholic University of Louvain, Belgium.
1964: Doctor of medicine, Karolinska Institute, Stockholm, Sweden.
1965: Doctor of science, University of Maryland.
1965: Doctor of science, New York University.
1965: Doctor of science, the Jefferson Medical College and Medical Center, Philadelphia.
1967: Doctor of science, Columbia University College of Physicians and Surgeons.
1968: Doctor of science, University of California (Berkeley).

Honors and awards:

1945: Harvey, lecturer.
1956: John F. Anderson, lecturer.
1958: Scientific Award for Outstanding Achievements in the Field of Renal Physiology, Malaria Control, and National Administration of Medical Research, New York University.
1961: The Mendel Medal Award, Villanova University.
1962: Public Welfare Medal, National Academy of Sciences.
1964: Rockefeller Public Service Award.
1965: Election to membership in the National Academy of Sciences.
1965: Honorary fellowship in American Association of Hospital Administrators.
1966: Public Health Service Distinguished Service Medal.
1966: The Modern Medicine Award for Distinguished Achievement in Medicine.
1966: Presidential Distinguished Federal Civilian Service Award.
1966: Honorary member, American Hospital Association.
1966: John M. Russell Award, Markle Foundation.
1966: Abraham Flexner Award, Association of American Medical Colleges.
1966: Alan Gregg, lecturer.
1968: Hadassah's Myrtle Wreath.

Mr. FLOOD. We will now be pleased to hear your statement, Dr. Shannon.

## GENERAL STATEMENT

Dr. SHANNON. Mr. Chairman and members of the committee, the aims and accomplishments of the specific activities supported by the 13 separate appropriations for the National Institutes of Health will be discussed by the director of the institute or division directly responsible for the activity. My comments are therefore devoted to general problems and will reflect the current deployment of our resources rather than what might be needed for the full exploitation of the opportunities before us.

The budget estimates for the fiscal year 1969 are Spartan in character. Overriding circumstances, resulting from national commitments elsewhere, have necessarily limited the President's estimates for NIH to the amounts that can be justified as essential if the medical research establishment of the Nation is to be maintained at an effective level and not be threatened with disarray and deterioration. The 1969 budget is based on 1968 obligations that are some $50 million lower than the amount appropriated by the Congress. The Budget thus continues to be responsible to the congressional directive that a conscientious effort be made to reduce expenditures. In fact, I believe that it is as lean a budget request as is possible without seriously curtailing the activities which it is designed to support.

The budget does provide for the orderly continuation of the major existing programs and will enable us to meet our existing commitments to the research community. With some rearrangement of plans, it will also allow a minimal expansion of a few of the most critical activities. Frankly, it is not a budget that makes me happy but it is a budget that maintains a critical mass of biomedical activity while we plan for the most effective deployment of resources when dollar constraints on these activities will be less severe.

Last year—because several members were new to this committee—I contrasted the tremendous advances that have been made in medicine with the tremendous gaps that still exist in our knowledge of biological processes and in our ability to deal with disease. And I

outlined the development of the NIH programs which are now contributing so significantly to narrowing these gaps. This year—because it is the last time that I shall appear before this committee to defend the NIH budget—I should like to talk briefly about the future directions of these programs and to point out some problems that require special attention within the framework of present budget limitations.

### POPULATION

One of the areas of research activity that has particular national significance is population control and fertility studies. Although exact figures are not available, it was estimated in 1950 that the world's population was 2.5 billion. By mid-1966, the estimate had risen to 3.4 billion—a 36-percent increase in 15 years. At this rate there will be between 7 and 8 billion people by the year 2000—which is only 32 years away. Many very serious economic, social, and geopolitical problems are raised by these figures—and by the probable geographical distribution of these staggering increases. These problems are not problems that fall within the purview of NIH and I do not propose to discuss them. Nor can policy decisions to deal with these problems be medical decisions; they must be social and political decisions. However, medical research will continue to contribute to this population explosion both by saving more babies and by keeping more older people alive. It also has a responsibility for developing an adequate science base for meaningful population control. Despite recent advances, readily acceptable and generally applicable antifertility techniques are not available.

Population control and fertility studies should not be solely concerned with their negative aspects. There is as great a need for solving the puzzling problems of infertility as the relatively much simpler problem of rampant fertility. The whole process of human reproduction is, in fact, very imperfectly understood. The successful unravelling of its mysteries would not merely solve problems of infertility and provide for both family planning and population control but would undoubtedly enable us to prevent many of the birth defects that now take such a tragic toll. Nevertheless, the problems created by an uncontrolled population expansion are of such severity that our major initial emphasis must be on this aspect of research on human reproduction.

### BEHAVIORAL SCIENCES

The whole field of the behavioral sciences also needs intensive exploration from a biomedical point of view. Questions concerning growth and development, the behavioral determinants of biological systems, individual behavioral pathology and social pathology, all fall within the joint domain of the social and medical sciences. The definition of health and the consequent domain of responsibilities of medical research have been considerably broadened over the past decades. They now include, in addition to the biological factors which contribute to health, the need to understand the emotional, intellectual, economic, and social factors which exert such a dominant influence on well-being. Yet the scientific basis for understanding many of these factors may be described as being in the same relatively primitive state

as was biological knowledge in the 1930's. There is an obvious need to incorporate the behavioral sciences—and, indeed, the broad spectrum of the social sciences—into the medical establishment. Such a move will have a broadening influence not only on research capability but on the educational experience to which developing physicians are exposed.

Heretofore, the major contribution to the support of the behavioral sciences has been limited to the National Institute of Mental Health. The establishment of NIMH as a separate bureau in the Public Health Service will not diminish the need for it to maintain its present role in the support of the behavioral sciences. However, the behavioral sciences also have increasing importance and relevance to the programs of other Institutes.

The National Institute of Child Health and Human Development provides avenues for developing many aspects of the behavioral field related to normal human growth and development. It has now become possible to support research and training programs in the emotional and intellectual development of the normal child in parallel with studies on biological development. An understanding of the learning process, cognitive processes, development of speech, and linguistics are significant areas of investigation. Similarly, the research and training of scientists in the field of aging—and the elucidation of the attendant intellectual, emotional, and social problems—are essential.

The National Institute of General Medical Sciences is responsible for providing a wide-ranging, discipline-oriented base for research and training in the behavioral sciences in order to underpin the more limited problem areas of each of the categorical Institutes. This Institute will stimulate the growth of behavioral science research and training in the medical schools and facilitate its inclusion in the core curriculum of medical education.

The regional medical programs also serve to focus attention on problems which have heretofore received insufficient attention—the sociology and economics of medical care, including questions of new medical care systems, problems of acceptance of medical information and services, needs of the physician as well as the patient, and the effects which affluence and education are having on the demand for medical services. All of these are relevant programs to the regional medical program.

### BIOENGINEERING

The third area that merits more purposeful development is the broad field of bioengineering which may be briefly defined as the application of the principles and techniques of the physical—and especially the engineering—sciences to medicine and to the problems in biomedical research leading to more effective diagnosis and treatment of disease. Dramatic examples of what has already been accomplished in this field are the development of an array of monitoring devices, automated laboratory devices, the so-called artificial kidney, the development of the heart-lung machine, the pacemaker, and artificial heart valves, and the work now in progress on the artificial heart. There are also many less publicized but equally important contributions of bioengineering to clinical care and to both clinical and laboratory research. However, the potentialities of this field have hardly begun to

be exploited. A systematic and vigorous pursuit of the application of engineering know-how—especially the recent advances in electronics, miniaturization, and the creation of new materials—can, I feel sure, bring about startling changes in diagnostic and therapeutic methods and in the organization of hospitals and hospital systems during the next 10 or 20 years.

In the fiscal year 1967 appropriations, this committee provided $250,000 for planning, consultation, and contractual assistance with a view to launching bioengineering development as "a distinct activity for which separate budgetary provision should be made." With these funds we awarded a contract to the National Academy of Engineering for a study which will examine the future role of engineering concepts and technology in advancing the understanding of biological systems; the development of instrumentation, diagnostic and therapeutic devices, artificial organs, and so forth; and the evolution of hospitals and health service units. Recommendations will also be made for converting the no man's land that lies between engineering and biomedicine into a recognized hybrid activity and for developing prototype institutions that can foster research and manpower development in this new field.

A first report on the results of this study is expected within the next month. It is, however, already clear that a beginning on a systematic and integrated program must be made now and the budget request, therefore, includes $1.3 million for this purpose. To defer the beginning of this activity—which is already long overdue—would be most unwise.

### RESEARCH INSTITUTES

Another aspect of the NIH programs that needs selective development is the creation of new institutional foci for research on broad problems that are particularly promising but which require a combination of scientific talent and facilities not commonly found even in the best of our medical schools and associated hospitals. The need for special research institutes for this type of activity is clearly defined in the Report of the President's Commission on Heart Disease, Cancer, and Stroke. But they are not only needed for the three disease areas covered by that report but also for the dental sciencies, for aging, for pharmacology, and toxicology, and for bioengineering—to mention only the more important areas. Such centers, which will provide a suitable setting for complex research activities and special science development, are essential if we are to move progressively to a more direct approach to the solution of service problems, now that a broad science base for a number of developmental activities has been established. A recent reexamination of our plans for expanding federally initiated programs for collaborative research on specific health problems—to which I shall come back in a moment—has clearly revealed that many of these projects will be greatly assisted by more purposeful programing but that it is unlikely that this can be done in the conventional university or medical school department without either distorting the project or distorting the total research and educational program of the institution. This is particularly true, for example, of the development of the artificial heart and, probably, in general of bioengineering projects; of the cardiovascular and stroke centers; of

the proposed fertility studies; and possibly of some of the behavioral studies that need to be undertaken. Provision will have to be made in the future for establishing research centers specially equipped, staffed, and located for the most effective pursuit of some of these sharply defined and carefully directed studies. They will also provide a new dimension in the training of a new type of scientist for the future. However, it must be emphasized that such activities cannot replace the broad base of scientific effort already established because this provides the fertile soil on which developmental opportunities grow.

### INSTITUTIONAL PROBLEMS

A more general problem—which is becoming urgent as a result of the mounting economic pressures on our educational institutions—is the need to make more realistic provision for maintaining the stability of the institutions in which the bulk of our medical research and research training must continue to be conducted. Federal support for these activities now plays such a major role in institutional financing, staff deployment, and program planning that even relatively minor shifts in Federal programs or restrictions in the availability of funds can have a major impact on these institutions. For example, we have found that the normal operation of our priority-scoring system, under the present availability of funds for competing research projects, threatens in some cases to wipe out all NIH support for a medical school department which has been heavily dependent on that support. This, in turn, has an indirect but profound effect on the educational system. Clearly, a more stable system of support—or, at least, one less subject to rapid fluctuation—must be established if some of our medical schools are not to be seriously harmed.

Indeed, the institutional problems of medical education should be a matter of urgent national concern and merit the most serious consideration. The responsibility of the medical schools and their faculties has broadened considerably since the early 1950's. Physician education has become more deeply rooted in fundamental science; there has been a rapidly expanding need to provide postdoctoral and specialty training; research has become more complex, more technologically demanding, more essential to the educational process, and much more expensive. These changes have created a need for more diverse skills on the part of the faculty; have to some extent outmoded the traditional curriculum for physician education; have placed great strains on the organization of the medical schools; and have weakened the bonds between the faculty, the institution, and the students.

These strains and stresses are now being compounded by the progressive involvement of the medical schools in organized research projects aimed at the achievement of nationally desirable goals and by the greater demands society is now making for the right of every individual to adequate health services irrespective of his economic status or the remoteness of his place of residence from centers of medical excellence. The growth of combined research and service programs in rehabilitation, mental health and mental retardation; expanded service programs for children; the development of comprehensive community health programs for economically disadvantaged groups; participation in the regional medical programs and in the partnership for

health; involvement in operational research on the development of more effective delivery systems for health care; and the obligations imposed by medicare and medicaid are now overburdening academic institutions that were initially designed for the relatively simple task of providing a well-ordered and traditional education but which are now being called upon to deal with a broad array of social problems.

We have given serious consideration to these institutional problems which vitally affect the NIH programs and we are in process of developing some proposals for their solution in association with the Bureau of Health Manpower.

REVIEW OF SPECIAL PROGRAMS

I have already referred to an intensive review which we have conducted during the past month or so of the federally initiated research programs sponsored by NIH. There are about 30 of these so-called organized rsearch programs. Our objective has been to review their present status, assess their potential growth, and to develop plans for their future development. These plans are not "blue sky" proposals but conservative projections based, first of all, on what it appears feasible actually to achieve and, secondly, on the 5-year targets that were approved by the Department last spring. If circumstances permit—that is, if financial constraints are relaxed—these reviews will provide a realistic basis for orderly program development in these areas during the next 4 or 5 years.

I should like to emphasize that these federally initiated programs are not being undertaken at the expense of the investigator-initiated research projects which have dominated NIH support up to the present time. They do not represent a change in NIH policy but an addition to NIH activities which should serve to provide a more effective approach to selected problems of major national importance that justify—or, indeed, require—more organized collaboration and programed activity than is characteristic of research conducted by individual investigators.

These federally initiated programs will not displace support for investigator-initiated research which must continue to be the main stream of biomedical research. The traditional research projects represent the consensus of the scientific community on what is important and what is feasible. This self-generated activity—with its mix of fundamental and applied research—will not only insure the vigorous pursuit of the widest range of opportunities for progress but must continue to provide the scientific underpinning for developmental projects and to point the direction for future targeted research.

The increased attention being given to these organized programs should also not be interpreted as representing any wavering of our firm conviction about the overriding importance of so-called basic research. In fact, the organized programs of today have been made possible by the basic research of yesterday. Their present feasibility and probability of success is directly proportional to the soundness and completeness of the fundamental research on which they are based. It follows, of course, that the feasibility of future "organized" or developmental programs will depend almost entirely on the scope and vigor of the fundamental research that we support in the intervening

years. It is certainly true in scientific research that you can't harvest what you don't first sow.

### HEART TRANSPLANT PROBLEMS

The difficulties that can be encountered as the result of gaps in fundamental research are now dramatically illustrated by the recent spate of heart transplant operations. While the purely surgical technique for such operations are already well developed, too little research has, as yet, been completed on tissue antigens, species differences in rejection phenomena, and organ differences in rejection in the same species. A great deal more knowledge is necessary before any of these operations can become an accepted form of treatment. In fact, the newly established Board of Medicine of the National Academy of Sciences issued a formal statement on February 28 describing these operations as a scientific exploration of the unknown and urging that only a relatively small number of careful investigations involving cardiac transplantation * * * be done at this time.

At the same time, the American College of Cardiology called a conference—tentatively scheduled to start on March 23 at Bethesda—to grapple with the problems arising from the development of techniques for heart transplantation. We are at present reviewing NIH activities on problems related to heart transplantation and considering how the necessary research can be accelerated, including relevant training and the provision of essential services. NIH should obviously take this task seriously and it will probably be necessary to redeploy some of our available funds to make a more concerted attack on these problems. We are also giving urgent attention to the moral and ethical issues raised not only by heart transplantation but by a number of clinical investigations involving human subjects.

### FOGARTY CENTER

I am happy to report that we are making good progress in developing plans for the John E. Fogarty International Center for Advanced Study in the Health Sciences for which this committee provided funds last year.

I am told the announcement of the establishment of the center will appear in the Federal Register this week.

We expect that a contract for architectural drawings will be awarded well before the end of this year. Meanwhile, we are making arrangements to renovate and remodel "Stone House" which is the large and attractive residence of the former owners of part of the NIH campus. It sits on the site selected for the Fogarty Center and it seems to us to be both practical and prudent to incorporate it into the overall design of the center. As renovation can probably be completed in about 3 or 4 months, it will be possible to bring some of the Fogarty Center activities into being much sooner than if everything had to wait for the completion of the new building. We expect that the conference program and the scholars' program can both be started early next year.

BUDGET SUMMARY

The $1,196,693,000 requested for fiscal year 1969 is distributed as follows among the five major activities of NIH: The $275.6 million requested for direct operations include $87.5 million for the conduct of research by the NIH scientific staff and $126.5 million for collaborative projects. The remaining $61.6 million is for other direct operations, program direction, administrative services and management of the extramural program.

On reading the statement, I think that $61.6 million is a rather large amount to put in the category of other. So if I could insert a breakdown of those figures at this time, it might be useful:

Biometry and epidemiology, $9.8 million; international research, $3.3 million; Fogarty Center, $0.6 million; division of computer research and technology, $4.8 million; the division of biologics standards, $8.5 million; training, $1 million; professional and technical assistance, $3.3 million; review and approval, $20.3 million, and for program direction, $10 million.

Of the $652 million requested for research grants, nearly $165 million is for the special research grant programs—including $53 million for general research support—and $342 million is for noncompeting research projects which we already have a commitment to support. This leaves $145 million for competing grant applications of which it is estimated that close to $91 million will be needed for supplemental awards for existing grants and for the renewal of projects to which continued support has not been committed. About $54 million will thus be left for the support of new grant projects—this is $6 million less than the amount appropriated for this purpose for fiscal year 1968.

The requests for training grants and fellowships total $197.8 million—an increase of $4.8 million over the fiscal year 1968 appropriation.

For health research facilities construction grants, $8.4 million is requested. In addition, $12.2 million will be carried forward from the fiscal year 1968 appropriation in accordance with the Bureau of the Budget's directive for curtailing fiscal year 1968 expenditures.

The request for the regional medical programs is $62.9 million. This activity will also have a carryover from fiscal year 1968 of $30.9 million. These are grant funds—an additional $6 million for this program is included in the figure for direct operations.

I believe that your review of these requests will confirm my earlier statement that this is as lean a budget as it is possible for us to present to you without a major cutback in programs whose only purpose is to benefit the people of this country by strengthening the ability of the medical profession to diagnose, treat, and prevent disease and disability.

REPORT OF COMMITTEE ON GOVERNMENT OPERATIONS

Mr. FLOOD. We have all heard and read in the newspapers and elsewhere in the news media about the report of the Committee on Government Operations, and many of us have read the report itself.

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Now, we have not heard or seen as much with regard to Dr. Shannon's comments on that report. You did not do very much to

see that your comments were widely distributed, in fact it almost appears that you have done the contrary.

Why in this case? Why are you hiding your light under a bushel?

Dr. SHANNON. Mr. Flood, a decision, in which we fully concurred with both PHS and the Department, was that the reply to the Government Operations Committee should not be by NIH but by the Department. For this reason it might be appropriate for Mr. Kelly to comment on the way the reply to Mr. Fountain was prepared and some of the departmental attitudes relative to that reply.

Mr. LAIRD. With all of the public relations people in the Department, you would think you would be able to get a little more recognition to your reply.

What about that, Mr. Kelly?

Mr. KELLY. Mr. Chairman, I am not sure we felt that the conduct of a dialog in the daily newspapers was the most productive way of advancing the public service and of assuring the Congress and the American people that the research program for the NIH and the PHS were being conducted in the most effective way.

Mr. LAIRD. By "we" I presume you mean the Department of Health, Education, and Welfare.

Mr. KELLY. I do, sir; and I think I speak collectively for the Director of the National Institutes of Health, for the Surgeon General and for Secretary Gardner and Acting Secretary Cohen.

Mr. LAIRD. But there has been a dialog within your own Department?

Mr. KELLY. There has indeed, and it was really an attempt on our part to do two things in preparing the response, copies of which were sent to this committee. One was to assure that the thoughtful reader of the subcommittee report and of our response would read the criticisms in the context of the problem that was presented to the Department of Health, Education, and Welfare, to the NIH in creating this research program and its operation. Secondly, was that it would reflect our most thoughtful considerations of the criticism that were made, the validity of them and the actions that we had taken, were taking or proposed to take in response to them.

I believe that the report does this. It is a very difficult answer to characterize because it was developed in high degree of detail on each of the recommendations. But I think that if you were to take my view of what the report says, it says that the Federal Government was presented——

Mr. FLOOD. Let me ask you this: What were the main points in the committee's report and the main points in your comments on the committee's report?

### MANAGEMENT ASPECTS OF THE REPORT

Mr. KELLY. Let me take the ones that I think I am probably the most competent to speak to and that is the business management aspects. In a very broad measure the Fountain committee concluded that in the development of the administrative management process of the relationship of the NIH with the grantee community, colleges and universities, that the NIH had not given adequate attention to (1) the problems of the review of costs, (2) the assurance that funds were

used for the purpose for which they were made available, (3) the proper measurement of indirect costs, and (4) the proper accountability of equipment and similar problems of administrative management nature.

I think that the Fountain committee report set forth a number of examples where there had been an overpayment, or an inadequate accountability of equipment.

And our answer, I think, said something like this: That there are two forms of the management that an agency is concerned with. The first is creating a system of management, an environment of management; and the second is dealing with management improvement, perfecting and improving the management as one becomes aware of its shortcomings or find ways in which improvements can be made.

And I believe that the NIH is to be given a great deal of credit for having created a management system which had the ability to accomplish its primary functions; that is, the stimulation and the development of a research capability in this country.

Mr. FLOOD. This was not something that you have done overnight?

Mr. KELLY. It was not and it was done under a period in which there was great stress and strain created by a rapidly enlarging program. And the things that you do well in creating management environment live with a program for many, many years, and the things you do poorly hurt you for a long time to come. This basic problem of how well you create a managerial system is probably the most important form of public administration, although I think public administration more nearly is measured by its management improvement techniques rather than by its management creation techniques.

Mr. FLOOD. What is a management system?

Mr. KELLY. The whole concept in the NIH (1) of using grants, (2) of having applications come in that are reviewed by study sections and panels, (3) of creating a relationship of reports to the Federal Government of the stewardship of those, and (4) of the conduct of audits. Further, the system involves the extent to which we would use, for example, the salary policies and the procurement policies of the grantee institution, based on a theory that they were partners. They were spending preponderantly non-Federal funds in the conduct of their business and the policies that govern the expenditure of their non-Federal funds would be the policies that would govern the expenditure of their Federal funds. Another example is that they would not deviate from their own salary policies in the use of Federal funds, and that we would not establish Federal salary policies for universities but rather universities shall use their own. These are all the creation of a system and relationship.

The management improvement techniques are the refinements and perfections and improvement on these as you find there is some faulty area or areas susceptible of perfection and improvement as you go along.

And this we will always be doing, making management improvements.

I think our finding was that the creation of the basic management system was very sound, but that in its development and in the expansion of its very large workload it had faulty aspects to it. Some of

the findings of the Committee on Government Operations identified some of these faults. They were very real ones. They did exist. There were some overpayments of indirect costs. There were some failures of property accountability. We have endeavored to correct these and to perfect and improve the managerial system in order to take into account the problems that were brought to our attention either by the Government Operations Committee or by the General Accounting Office or by our own audit staff. I think the report makes a serious effort to identify the extent to which we have already taken corrective action; the extent to which the concerns of the committee do not now exist; the extent to which we are already on top of the problem of establishing indirect cost ratios; conducting and acting on audits on a reasonably current basis; and other management areas.

Mr. FLOOD. You are obviously satisfied that a major thrust of the Government Operations Committee was in the area broadly of management systems, and that one of your major counterthrusts in turn was in the area of management.

Dr. SHANNON. Mr. Flood, I would like to interject two other thoughts here. Mr. Kelly started off by saying he would address himself to those aspects of the report that he was not familiar with, and indeed he has direct responsibility for a good many of these aspects of management at the present time.

The report covers two other broad areas of equal, perhaps even greater, significance. One purported to show that when we established novel programs we did not do this prudently or in the best public interest. We tried in our reply to show that we did, indeed, do it in the only way possible if we were to satisfy the public interest.

QUALITY OF RESEARCH

The other purported to show a progressive decrease in quality of research as the sums available to the medical sciences increased.

Mr. FLOOD. Quality of performance?

Dr. SHANNON. Yes, sir. Actually, the figures that were used were the priority scores assigned to research grant applications. We have gone from a very small program in 1956, when the research grant program amounted to $40 million, to one in 1966, which was the last figure that the committee used, when it was more than $600 million. During those initial years, when very little work was supported, the shortage was such that only a very limited number of investigators received support. It was only after additional funds began to be put in that the process of assigning prorities, in terms both of the applications reviewed and of the grants actually made, was stabilized. If anything, there was an increase in quality rather than a decrease.

If we can lick, as I think we can—and I think we largely have—the management aspects of a very complex program such as this, the judgment as to whether it is good or bad should depend wholly upon the quality of the product we produce. The claim of a lessening in quality was perhaps the most severe criticism in the entire report and I do not believe that the figures cited bore this out. In our reply we attempted to show why we disagreed with the committee.

Three large areas are involved: Prudence in the development of new programs, the quality of the product that we support, and the

evolution of suitable management techniques to assure proper accountability on the part of grantee institutions. These are the three major areas, sir.

Mr. FLOOD. We have the impression this is going to take a great, great deal of study and the last word has not been said by your people in reply to the report, and, I would guess, the last word has not been said by the Government Operations Committee, either.

SYSTEM FOR FUNDING MEDICAL RESEARCH

The same basic system, Dr. Shannon, of funding medical research has been followed for many years. During that period the funds available, everything connected with the program, including the cost of processing the ever-present paperwork has pretty greatly expanded.

Do we need to change this system? What do you think about that?

Dr. SHANNON. Mr. Flood, the system may give the appearance of being constant but indeed it is not. It is subject to continuous change and continuous improvement.

In terms of cost, when you get to a given critical level—I would say that in the research area this could be around $250 or $350 million—further incremental increases will not be accompanied by a reduction of unit cost.

I believe that you will find that our processing costs have remained relatively stable over a substantial period of time if they are taken in proportion to the dollar amount of the program. In view of the experience of other granting agencies, I believe that this is probably a reasonable basis for projection into the future.

You can look at it in any one of a variety of ways. You can look at other Government agencies and their costs or you can look at large private foundations, that do pretty much the same type of thing, and their costs. We would say that our costs, in general, compare favorably with most of the others.

Mr. FLOOD. But you don't feel the basic system for funding that NIH has been following is rigid or frozen? You think it is sufficiently elastic.

Dr. SHANNON. Indeed, Mr. Flood, it is elastic. I mentioned that we have some 30 special program areas. The two largest ones are in the Cancer Institute—cancer chemotherapy and cancer virology. The two next largest ones are the perinatal program in the Neurology Institute and vaccine development in the Allergy and Infectious Diseases Institute. It turns out that quite different management techniques, not surprisingly, are required for such federally initiated research than for investigator-initiated research. Different management systems have to be developed for different types of programs. We find also that such grants as general research support grants, which I believe in this budget amounts to $60 million in round figures, require other systems of management because here the grantee is the institution and the purpose of the grant is quite different.

Mr. FLOOD. Do all of these new creatures merge into the basic system of funding medical research?

Dr. SHANNON. Indeed, they do. New programs have been developed to overcome deficiencies, to provide specialized resources, to provide stability of institutions or to provide for developmental research to

take advantage of opportunities that have emerged from basic research. It is rarely possible to take a management tool that is already in existence and simply apply it in a new area.

Mr. FLOOD. This testimony, especially coming from you, after such an illustrious career, is a matter of primary importance to us. Can we continue to use this vehicle? Is it sufficiently elastic?

HEALTH SCIENCE ADVANCEMENT AWARD

Dr. SHANNON. It is not monolithic and does not remain constant. Let me give you an illustration of a very complex program that the Government Operations Committee went into in some detail, and that is the Health Science Advancement Award.

Mr. LAIRD. That is a pretty important program.

Dr. SHANNON. Yes. The purpose was to help an institution that already had some excellence to broaden its capability for the training of new scientists. The Bureau of the Budget, as a result of discussions with the Senate Appropriations Committee, put $1 million in the budget on a trial basis to enable us to undertake this program on an experimental basis in order to determine how this could be brought about.

Mr. Flood, you must realize that we have an enormous fund of information on institutions across this Nation—their scientific capability, their scientific needs, and so on. There are about 90 medical schools and 40 universities that could compete for these funds and we had $1 million. It was also apparent that, if these funds were to do any good, we should have to provide stable funds for about 5 years. We felt we might be able to greatly improve two, or perhaps three, academic institutions with the $1 million available.

On the first go-around we were not satisfied that we had adequate criteria for the program. It was therefore deferred for a year. It finally came down to four institutions. I would prefer not to name them for the record. We selected two and assisted the third by another device and turned down the fourth.

In the next go-around, when we had $3 million available, we had had the experience of negotiating with four institutions during a period of approximately a year and had had many discussions with other institutions. We knew, from our conversations, that the number of institutions who were anxious to take advantage of these funds was tremendous. We knew that they wanted these funds for staff development, for construction, for new departmental development, for a great variety of things. So the management technique we developed was to send a letter to essentially all our grantee institutions informing them that money was available for the coming year and saying, at this time, we did not want an application but a letter of intent to apply for these funds, giving in some detail what they wanted to do but not making positive commitments. The deadline given was about 2 or 3 months hence. We received 128 letters of intent. We set up a technical committee that took those letters and through a process of elimination, reduced the 128 to 30 and then reduced the 30 to about 15. Those 15 institutions were asked to apply, and of the 15, six received the award.

Mr. FLOOD. This was done under the basic system of funding for medical research?

Dr. SHANNON. This was done under the basic system of funding for medical research. For the program designed to help a school to attain a higher level of excellence, this particular system was developed to meet this particular need. Next year we will be in a better position to be more positive about what can be done with these funds, what restrictions must be imposed, and so forth. The point I am trying to make is that we had to evolve a system to satisfy a unique need. There was no pattern already existing.

Mr. FLOOD. And it did not destroy the fabric of the basic system?

Dr. SHANNON. No, sir.

Mr. SMITH. But some institutions which were already considered to be at a high level of excellence were selected.

Dr. SHANNON. The basic definition of the problem was not to create excellence de novo, but to take excellence already existing and broaden it so that science training could be substantially improved over a broader area. This program was not meant to satisfy a general need or simply to broaden the geographical distribution of support. In other words, those funds had to be used effectively for the purpose for which they were appropriated.

Mr. SMITH. You were not trying to bring those in the lower levels of excellence up, but you were taking those from the top and improving them even more?

Dr. SHANNON. No, sir. The conviction of those concerned with the advancement of medical research is that we have in this Nation about 25 wholly adequate, highly qualified universities—and that is about all—and that this Nation would be better off if we could increase that number from 25 to about 50 in the next 10 years. It was for doing this type of thing that these funds were requested and for which they were expended. We fully appreciate the need for helping inadequate institutions to bring them to the level of competence. But we feel this has to be done through different techniques with funds specifically made available for that purpose.

The guidelines have to be totally different depending on whether you are trying to enhance quality or are trying to develop competence. You can have a medical school, for example, with a very modest research program, but an adequate one, without having that medical school commit itself to a large number of social projects and graduate programs. It still can turn out very high quality physicians and we need those schools. But the technique of developing that type of institution is different from developing multipurpose high-quality institutions for a wide range of research, graduate education, and social service.

### COST OF REVIEW AND APPROVAL OF RESEARCH GRANTS

Mr. FLOOD. In the total for NIH what is the cost of review and approval of research grants including the cost of the study sections, the advisory councils, et cetera?

Dr. SHANNON. I cannot give you that figure. I can give you the cost of the mechanical handling of the review process. When you talk about the process itself, that involves every Institute Director and my entire staff and their salaries will appear under the general heading of program direction.

Mr. FLOOD. We are speaking of the research grants and we would like to see the costs of the process within NIH.

Dr. SHANNON. $20,285,000.

Mr. FLOOD. That is a ball park figure?

Dr. SHANNON. That is the budget figure for "Review and approval."

SLOAN-KETTERING GRANT

Mr. FLOOD. How has the Sloan-Kettering grant worked out?

Dr. SHANNON. I think very well. I would like to make a general statement on it but not get into a substantive discussion of it because it is a matter for the Cancer Institute. I feel responsible for that mechanism because 6 or 7 years ago I first proposed that the Cancer Institute explore the use of a single instrument——

Mr. FLOOD. By a single instrument you mean making a single grant?

Dr. SHANNON. A single grant or contract, one or the other.

Mr. FLOOD. How long has this idea been effective at Sloan-Kettering?

Dr. SHANNON. This is the third year.

Mr. FLOOD. Have you been able to get the feel of it in that time?

Dr. SHANNON. I think so. In the first place, this is an institute very similar to our own Cancer Institute and about the same size as its intramural operation. I can submit for the record a schedule showing how it was being supported in 1965.

(The schedule follows:)

SKI—SINGLE INSTRUMENT OF SUPPORT

Total grants and contracts closed out as of December 31, 1965: $4,358,355 (details below).

Amount of first single instrument award January 1, 1966: $4,314,504.

*Grants and contracts closed out, Dec. 31, 1965*

| | |
|---|---|
| Research grants: | |
| NCI (23) | $1,931,675 |
| NIAMD (5) | 121,344 |
| NICHD (2) | 43,742 |
| NHI (3) | 52,223 |
| Rad Health[1] (1) | 31,489 |
| GRS (1) | 415,924 |
| Training grants: | |
| NCI (1) | 215,000 |
| NIGMS (1) | 28,004 |
| Contracts: NCI (3) | 750,000 |
| RCA and RCDA: | |
| NCI (8) | 158,080 |
| NIAMD (1) | 12,617 |
| Pending applications ready for payment: | |
| NCI (2) | 43,331 |
| NIDR (1) | 23,183 |
| Center grant adjustments: NCI (2) | 531,743 |

[1] Not NIH.

Dr. SHANNON. The sole purpose of this Institute's existence is to find ways and means to better diagnose cancer and to provide better therapy.

Mr. FLOOD. With reference to review and approval of research grants, would this approach lend itself to saving money?

Dr. SHANNON. Oh, yes; it would. The unique thing in this institute is that it is wholly a research institute with no basic educational function. Our funds represented about 50 perecent of its operating funds and the other 50 percent came from private sources. Over 5 years we found that for each year 50 percent was from us. Programs went in and out but the proportion remained approximately the same.

Our study sections are not used to reviewing total institutions. They review individual research grants in competition with others. But it is possible to put together a technically competent advisory group to do this review, and this is what was done.

Mr. FLOOD. Do you have any more proposals similar to this type of operation?

Dr. SHANNON. We have given 15 or 20 planning grants and at the present time proposals are beginning to come in. I would be very much surprised if we didn't find it more scientifically rewarding to review them on the basis of the total institution rather than the individual pieces that make up the total institution. We have no proposals today.

FINANCIAL PROBLEMS OF MEDICAL SCHOOLS

Mr. FLOOD. There has been some comment since we started the hearings on public health concerning the use of research and training grants to help medical schools with their very critical and complicated financial problems. Every now and then the word "subterfuge" crops up. Do you want to comment on this word "subterfuge" in connection with these grants?

Dr. SHANNON. I will be very glad to. I do not think there is any subterfuge.

Mr. LAIRD. Maybe that is not a very good term.

Dr. SHANNON. Let us take subterfuge out and see how the system works in the educational environment.

An institution in general has three functions and these functions, in one way or another, are shared by every institution. There is research, the instructional process, and the performance of some service or some activities related to service. A physician who heads a service, one perhaps that relates in large measure to cancer surgery, can look at a patient in three lights, as a subject for teaching the undergraduate medical student; or as service to his community, if he provides this patient with surgical treatment; or as a straightforward research operation.

Mr. FLOOD. Research and training?

Dr. SHANNON. Many of the things that go on in the medical schools just cannot be pulled apart. You cannot say, "This is research, this is instruction, and this is service." Many things do have dual purposes. I don't think a scientist can sit in a scientific environment without having an overall obligation. He has to be able to talk in seminars and he has to have consultation with his colleagues. In other words, the give-and-take in an educational environment also takes his time. Are you going to say that this is service to the environment or say that is the only way the man can take advantage of that environment for his own work?

I think that is the only answer I can give you. The point I want to make is that when funding primarily for research purposes approxi-

mates something like 50 percent of the funding of an institution, it is difficult to get a clear separation of its activities and be able to certify that $x$ dollars was for this and $y$ dollars was for that. It creates an impossible situation to ask a man to divide himself up in three parts. I think he does this as honestly as he can. He may be able to say he spends half his time in research, or 75 percent of his time in research, and the rest of his time in other activities. I do not know of any way to get a better accounting than that, as long as you have multiple activities.

Mr. FLOOD. You know what is developing in the hospital world and in the medical school world. We are developing a new breed of administrators. Sometimes they are doctors and sometimes not. This is a separate breed from the one you are talking about.

Dr. SHANNON. The funds over which the administrator has control are the funds for general research support activities. It is our conviction that these are the most important funds spent in medical schools today. Our reports on these expenditures show that they fall, generally, in a limited number of categories. They are used to supplement staff salaries; they are used to introduce young students to the research process; they are used for multiple scientific activities.

Mr. FLOOD. We will recess until 10 o'clock tomorrow morning.

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FRIDAY, MARCH 15, 1968.

## APPLICATION OF RESEARCH RESULTS

Mr. FLOOD. Dr. Shannon, we frequently hear it said that research results aren't made available to those who should have them soon enough. What do you know or see as a weakness in this regard and what do you think we could do to correct the situation, if it exists?

Members of Congress get an awful lot of mail about this. Is this grossly exaggerated or what?

Dr. SHANNON. Well, Mr. Chairman, it is and it is not. I believe that reseach results in the large medical centers are applied immediately, but the system for the dissemination of information and, indeed, the actual delivery of medical services to various segments of our population is not such that all the American people benefit equally from the results that are available.

Mr. FLOOD. These are not practitioners.

Dr. SHANNON. I say where you do have the instructors and professors, these things are applied.

I would point out that two broad programs are aimed at bringing the benefits of research to the American people at large. As a matter of fact, three. There is, first, the regional medical programs which will attempt—and, I hope, successfully—to upgrade the capabilities of those who deliver medical services across the Nation wherever such service systems exist.

There are other areas of the Nation where systems don't exist. Some of the activities of the Office of Economic Opportunity are aimed at providing those services by other devices.

Then, as an umbrella for the State as a whole, dealing with the problems through its own lines of authority, there are the comprehensive health service programs.

Finally, there is now in the process of developing a request for authorization to establish active research programs on how medical services can best be delivered under different local circumstances.

Mr. FLOOD. What would this proposed research program be directed at?

Dr. SHANNON. Research on delivery systems.

Mr. FLOOD. What do you mean by a delivery system?

Dr. SHANNON. Before World War II a physician's capability depended much more than it does now on what knowledge he possessed himself, what laboratory procedures were immediately available to him in his own office, and what therapies could be delivered by him.

As the practice of medicine has become more complex and as more powerful tools have become available, a whole array of ancillary medical personnel has been brought into being to deliver all of the knowledge that is available to the point of use—namely, to the sick person. This now involves many more people than before World War II. It now involves the technical staffs of hospitals, clinics, diagnostic laboratories, and other paramedical personnel as well as medical personnel.

In some areas these are very well organized.

Mr. FLOOD. This is part of the problem and I insist on using this analogy: During the war the Defense Subcommittee had to urge the military to get away from the drawing board. "We need aircraft, bombers in England last night; not plans and not designs, but aircraft. We need bombers this morning. Let's get away from the drawing board for a while."

Now, what about getting the results of your research to the bedside? This is one part of the problem.

Dr. SHANNON. The programs I spoke about are directly related to that. Rather than using your analogy, I would prefer another that I think is more pertinent and that is the relationship between the land-grant colleges and the Agricultural Extension Services developed after the Land Grant College Act of 1862. During the following decades American agriculture was revolutionized by the development of new knowledge and its immediate application through the county-agent system in the Nation. Basically, there was a system for delivering knowledge to those who could use it on a day-to-day basis.

Mr. FLOOD. Now, let's get back to my question: Is this delay between research results and delivery grossly exaggerated? Are researchers getting their stuff to the bedside?

Dr. SHANNON. They are getting it to the bedside where they have contact with the patient. In other words, these cures or diagnostic resources are not locked up in books; they are not on the shelf, not being used. The point is they are not being used generally across the Nation, but only in those areas that have sophisticated hospital settings. The aim is to provide a more sophisticated hospital setting accessible in

wider areas and to provide a process for continuing education so the practitioners can use the information.

EFFECT OF HOUSE JOINT RESOLUTION 888 ON NIH

Mr. FLOOD. What has been the effect of House Joint Resolution 888 on NIH?

Mr. SEGGEL. Our obligational authority was reduced by $60 million under the Department plan for reductions in obligations and expenditures as required by the joint resolution.

Mr. FLOOD. That includes construction?

Mr. SEGGEL. That includes amounts carried over to 1969 for construction grants and regional medical programs. We have reductions in the areas of research grants, personnel costs, travel and related operating expenses that amount to some $16 million.

Mr. FLOOD. Did the resolution draw blood?

Mr. SEGGEL. Well, some blood; yes, sir, but we are absorbing the reduction. However, we understand that we are going to get about $4 million to cover our increased pay costs as a result of the pay act.

Mr. FLOOD. There is a transfusion on the way.

Mr. SEGGEL. For that purpose. That was an added cost for which we did not budget.

Mr. FLOOD. I wanted the record to show the effect of House Joint Resolution 888, because of the current keen interest in economy.

FUNDED AND UNFUNDED LEVELS OF APPROVED GRANTS IN 1966–69

Now, for the record, will you give us the number and the dollar value of approved research projects that you did not have the funds to finance in 1966 and 1967 and the estimates for 1968 and for 1969? Assume the budget figure for 1969.

Also, there is an awful lot of interest among the Members of the House and a good many other people in the funding levels for training and fellowships. So, show the same figures for these grants. Arrange the figures on all three categories, research, training, and fellowships—by institute.

Mr. SEGGEL. We will supply it for the record.

(The information follows:)

## YEAR END STATUS OF EXTRAMURAL PROGRAMS

### RESEARCH GRANTS—REGULAR PROGRAM[1]

[Dollar amounts in thousands]

| | 1966 | | 1967 | | 1968 estimate | | 1969 estimate | |
|---|---|---|---|---|---|---|---|---|
| | Number | Amount | Number | Amount | Number | Amount | Number | Amount |
| Cancer: | | | | | | | | |
| Funded | 1,453 | $54,228 | 1,210 | $57,267 | 1,218 | $60,516 | 1,205 | $62,953 |
| Unfunded | 155 | 5,517 | 148 | 4,583 | 120 | 4,774 | 110 | 4,965 |
| Heart: | | | | | | | | |
| Funded | 2,171 | 81,710 | 2,032 | 88,473 | 1,768 | 86,008 | 1,621 | 86,771 |
| Unfunded | 26 | 641 | 100 | 4,220 | 252 | 8,500 | 269 | 10,230 |
| Dental: | | | | | | | | |
| Funded | 339 | 11,263 | 314 | 10,792 | 297 | 10,919 | 288 | 10,990 |
| Unfunded | 82 | 2,165 | 54 | 1,482 | 61 | 2,616 | 97 | 3,910 |
| Arthritis: | | | | | | | | |
| Funded | 2,796 | 75,204 | 2,490 | 81,408 | 2,276 | 83,706 | 2,346 | 86,617 |
| Unfunded | 291 | 7,600 | 246 | 6,240 | 440 | 14,165 | 469 | 16,000 |
| Neurology: | | | | | | | | |
| Funded | 1,676 | 54,495 | 1,641 | 60,169 | 1,605 | 65,147 | 1,612 | 68,403 |
| Unfunded | 198 | 5,215 | 31 | 722 | 19 | 408 | 209 | 6,959 |
| Allergy: | | | | | | | | |
| Funded | 1,348 | 38,271 | 1,281 | 42,776 | 1,384 | 45,445 | 1,485 | 48,688 |
| Unfunded | 278 | 7,077 | 155 | 4,613 | 205 | 7,102 | 267 | 8,762 |
| NIGMS: | | | | | | | | |
| Funded | 1,684 | 53,612 | 1,620 | 63,388 | 1,432 | 70,128 | 1,544 | 74,822 |
| Unfunded | 450 | 14,031 | 450 | 17,282 | 452 | 17,989 | 470 | 21,139 |
| NICHD: | | | | | | | | |
| Funded | 1,065 | 34,136 | 1,072 | 36,674 | 1,122 | 37,583 | 1,122 | 37,583 |
| Unfunded | | | 104 | 3,863 | 222 | 8,895 | 318 | 12,731 |
| DEHS: | | | | | | | | |
| Funded | | | 81 | 3,699 | 92 | 5,064 | 95 | 5,071 |
| Unfunded | | | | | 15 | 861 | 17 | 1,000 |
| GRS-OIR: | | | | | | | | |
| Funded | 129 | 384 | 138 | 364 | 182 | 4,101 | 172 | 5,520 |
| Unfunded | | | | | 14 | 978 | 25 | 1,125 |
| Total NIH: | | | | | | | | |
| Funded | 12,661 | 403,303 | 11,879 | 445,010 | 11,376 | 468,617 | 11,490 | 487,418 |
| Unfunded | 1,480 | 42,246 | 1,288 | 43,005 | 1,800 | 66,288 | 2,251 | 86,821 |

### TRAINING GRANTS

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cancer: | | | | | | | | |
| Funded | 323 | $10,534 | 180 | $12,015 | 193 | $11,350 | 190 | $11,641 |
| Unfunded | 4 | 332 | 5 | 135 | 19 | 1,317 | 31 | 2,454 |
| Heart: | | | | | | | | |
| Funded | 400 | 17,446 | 396 | 17,752 | 385 | 17,696 | 368 | 18,150 |
| Unfunded | 8 | 239 | 12 | 376 | 18 | 900 | 29 | 1,850 |
| Dental: | | | | | | | | |
| Funded | 104 | 5,150 | 108 | 5,398 | 97 | 5,469 | 96 | 5,609 |
| Unfunded | 7 | 234 | 4 | 86 | 11 | 583 | 10 | 1,016 |
| Arthritis: | | | | | | | | |
| Funded | 321 | 14,204 | 309 | 14,855 | 303 | 15,706 | 309 | 16,109 |
| Unfunded | 2 | 86 | 10 | 367 | 33 | 1,814 | 52 | 3,000 |
| Neurology: | | | | | | | | |
| Funded | 483 | 17,619 | 469 | 18,515 | 519 | 18,780 | 516 | 19,262 |
| Unfunded | | | | | 23 | 3,390 | 67 | 7,513 |
| Allergy: | | | | | | | | |
| Funded | 184 | 9,058 | 189 | 8,916 | 164 | 9,251 | 162 | 9,488 |
| Unfunded | 3 | 83 | 4 | 204 | 3 | 132 | 17 | 1,002 |
| NIGMS: | | | | | | | | |
| Funded | 657 | 41,375 | 674 | 43,735 | 637 | 45,729 | 614 | 46,901 |
| Unfunded | 59 | 2,948 | 122 | 5,126 | 97 | 6,455 | 120 | 8,500 |
| NICHD: | | | | | | | | |
| Funded | 128 | 8,298 | 143 | 9,279 | 134 | 9,762 | 138 | 10,012 |
| Unfunded | | | | | 15 | 652 | 24 | 1,687 |
| DEHS: | | | | | | | | |
| Funded | | | 47 | 3,693 | 56 | 3,795 | 57 | 3,892 |
| Unfunded | | | | | 4 | 265 | 5 | 327 |
| GRS-DRFR: | | | | | | | | |
| Funded | | | 6 | 245 | 7 | 318 | 7 | 326 |
| Unfunded | | | | | 3 | 171 | 5 | 259 |
| Total, NIH: | | | | | | | | |
| Funded | 2,600 | 123,684 | 2,521 | 134,403 | 2,495 | 137,856 | 2,457 | 141,390 |
| Unfunded | 83 | 3,922 | 157 | 6,294 | 226 | 15,679 | 360 | 27,608 |

YEAR END STATUS OF EXTRAMURAL PROGRAMS—Continued

FELLOWSHIPS

[Dollar amounts in thousands]

| | 1966 | | 1967 | | 1968 estimate | | 1969 estimate | |
|---|---|---|---|---|---|---|---|---|
| | Number | Amount | Number | Amount | Number | Amount | Number | Amount |
| Cancer: | | | | | | | | |
| Funded | 359 | $3,380 | 248 | $3,171 | 329 | $4,326 | 326 | $4,422 |
| Unfunded | 48 | 513 | | | | | | |
| Heart: | | | | | | | | |
| Funded | 452 | 6,094 | 395 | 6,508 | 428 | 7,439 | 413 | 7,604 |
| Unfunded | | | | | | | 42 | 786 |
| Dental: | | | | | | | | |
| Funded | 120 | 1,442 | 113 | 1,552 | 143 | 1,971 | 138 | 2,015 |
| Unfunded | | | | | | | | |
| Arthritis: | | | | | | | | |
| Funded | 435 | 5,522 | 433 | 6,077 | 462 | 6,591 | 472 | 6,737 |
| Unfunded | | | | | 65 | 1,000 | 98 | 1,500 |
| Neurology: | | | | | | | | |
| Funded | 216 | 3,093 | 237 | 3,434 | 219 | 3,805 | 229 | 3,889 |
| Unfunded | | | 9 | 70 | 25 | 219 | 105 | 1,011 |
| Allergy: | | | | | | | | |
| Funded | 264 | 3,424 | 251 | 3,447 | 277 | 4,267 | 273 | 4,362 |
| Unfunded | | | | | | | | |
| NIGMS: | | | | | | | | |
| Funded | 2,346 | 18,441 | 2,395 | 19,400 | 2,215 | 20,910 | 2,249 | 21,373 |
| Unfunded | 570 | 3,565 | 984 | 6,572 | 1,031 | 6,986 | 1,020 | 6,860 |
| NICHD: | | | | | | | | |
| Funded | 216 | 2,858 | 262 | 3,724 | 269 | 4,102 | 275 | 4,193 |
| Unfunded | | | | | | | | |
| DEHS: | | | | | | | | |
| Funded | | | 15 | 99 | 16 | 100 | 21 | 200 |
| Unfunded | | | | | | | | |
| GRS-DRFR: | | | | | | | | |
| Funded | | | 5 | 41 | 20 | 200 | 20 | 204 |
| Unfunded | | | | | | | 10 | 107 |
| GRS-OIR: | | | | | | | | |
| Funded | 166 | 1,199 | 165 | 1,200 | 154 | 1,380 | 176 | 1,411 |
| Unfunded | 16 | 136 | 25 | 223 | 48 | 432 | 50 | 450 |
| Total NIH: | | | | | | | | |
| Funded | 4,574 | 45,453 | 4,519 | 48,653 | 4,532 | 55,091 | 4,592 | 56,410 |
| Unfunded | 634 | 4,214 | 1,018 | 6,865 | 1,169 | 8,637 | 1,325 | 10,714 |

[1] Excludes special research grant programs with unfunded applications totaling $5,035 in 1966, $8,780 in 1967, $12,963 in 1968, and $39,464 in 1969.

FELLOWSHIPS

Dr. SHANNON. I would like to comment on that if I may because you might like us to enlarge that insertion.

The fellowship pool, insofar as it affects the development of scientists in the Nation, is not clearly identifiable with a single agency. In other words, there is some overlap between NIH, NSF, and the Office of Education and NASA. The Office of Education cut their fellowships in half. NSF cut theirs back and NASA cut theirs back. Actually ours were not cut back substantially. There were just minor amounts.

Mr. FLOOD. What I hear are mostly complaints from the general public and the members about cutbacks in research.

Dr. SHANNON. And fellowships.

Mr. FLOOD. But that comes mostly from the academic area.

Dr. SHANNON. The complaints wouldn't be against any one agency, but the aggregate of all agencies.

Mr. FLOOD. We know there is a war on. We know there is going to be tight money and we know the budget should be balanced and we are in favor of that. But now I am hearing the other side from all these people—these are honest people now; they are sincere, dedicated,

honest people; they come to Washington at their own expense; and they agree we need economy, but they always wind up with "But don't touch me," whatever their little specialty might be.

Dr. SHANNON. Mr. Flood, could I add another "but" to that?

Mr. FLOOD. Sure. Capital B, capital U, capital T. I always hear it, "But."

Dr. SHANNON. I would suggest that you permit us to put in the record those areas of research that are ripe for program development at the present time but that cannot be touched under the budgets.

Now, we are not asking for any relief, but I think that if the public understands the areas that cannot be touched under the budget, then, I think, they will be more reconciled to the funds available for the programs in which they are interested. They will realize that this is truly a spartan budget, that there are many other areas where, under other circumstances, we would be pushing on more rapidly.

Mr. FLOOD. A lot of Members in the House get an awful lot of mail from constituents in the academic and scientific world, from universities and colleges in their districts. This is one area that will surely draw questions when the bill gets to the floor of the House.

Dr. SHANNON. I think the record would be strengthened if it were possible to show not only what is being done, or what is proposed in these appropriations, but what cannot be done. The case should be made that these programs are not growing because of fiscal restraints, rather than because of a lack of scientific need.

## ORGAN TRANSPLANTS

Mr. FLOOD. You touched on the subject of transplants at some length in your affirmative statement and you are also placing in the record a statement from the National Academy of Sciences dealing with the general subject of transplants. This, of course, has become a matter of tremendous national and I presume international concern because of the way news media of all types have handled these South African cases.

Then Dr. Barnard, himself, was in town last week for a couple of days. I had lunch with him, incidentally. He is a very fluent fellow, among other things, which is good.

I also have before me from the Department of Health, Education, and Welfare, dated January 9, 1968, a memorandum to the Surgeon General from you, Dr. Shannon, the Director of NIH.

A report for the week ending January 5, 1968, "Research Developments" is the title. This has to do with successful liver transplants in four patients. If there is no objection, I think this should be included following the National Academy of Science memorandum on the general subject of transplants.

(The documents referred to follow:)

[News from the National Academy of Sciences, Feb. 28, 1968]

### BOARD ON MEDICINE RECOMMENDS CRITERIA FOR HEART TRANSPLANTS

WASHINGTON, D.C.—The Board on Medicine of the National Academy of Sciences issued today the attached public statement, which proposes a set of guidelines on the undertaking of heart transplants.

The Board on Medicine was formed by the Academy in November 1967, to study the social functions of medicine. Composed of representatives of both medical

and nonmedical fields, its chairman is Dr. Walsh McDermott, Livingston Farrand, professor of public health, and chairman of the department of public health, Cornell University Medical College. Within the purview of the Board are such questions as how to improve the quality and delivery of medical care; how medical knowledge gets used, refreshed, and taught; the ethical and legal implications of human experimentation; and the role of medical schools and other biomedical institutions in attacking the medical problems of rural and urban slums.

### *Cardiac Transplantation in Man*

(By the Board on Medicine, National Academy of Sciences)

Progress in medicine depends largely on the cautious extension to man of a body of carefully integrated knowledge derived from programs of basic and developmental research in the laboratory. Extension to man is itself an investigative process that must meet the same meticulous scientific standards that obtain in the laboratory, and the extension can appropriately be started only when the total body of knowledge has reached a certain point. It is clear that this point has been reached in the case of cardiac transplantation.

Careful, detailed laboratory investigations in a number of centers have demonstrated the feasibility of a surgical technique for cardiac transplantation. With the skillful use of immunosuppressive agents, investigators have succeeded in maintaining the life of laboratory animals subjected to cardiac transplants for periods up to a year or more. Moreover, considerable relevant knowledge has been acquired from carefully controlled clinical investigations involving the transplantation of a kidney in a human being.

But, in contrast to the transplant of a paired organ of man such as the kidney, cardiac transplantation raises new, complex issues that must be faced promptly. In the case of a kidney transplant, the donation of the organ is not crucial to the donor; in the event of failure, the recipient may be kept alive for extended periods until another attempt is made. In the case of cardiac transplantation, the life of the donor cannot be maintained. Further, the recipient's life cannot be salvaged if the transplanted heart does not function. Highly important is the fact that the length of time that the recipient can survive is as yet conjectural, even if the immediate result is favorable as indicated by prompt resumption of function by the transplanted heart. Thus the procedure cannot as yet be regarded as an accepted form of therapy, even an heroic one. It must be clearly viewed for what it is, a scientific exploration of the unknown, only the very first step of which is the actual surgical feat of transplanting the organ. In this connection, it is clear that there are considerably more institutions whose staffs include men with the surgical expertise appropriate for the first step of the investigation—the actual transplantation—than have available the full capacity to conduct the total study in terms of all relevant scientific observations.

Because of these special circumstances it is the considered view of the Board on Medicine of the National Academy of Sciences that for the present, cardiac transplantation should only be carried out in those institutions in which all of the following criteria can be met:

1. The surgical team should have had extensive laboratory experience in cardiac transplantation, and should have demonstrated not only technical competence but a thorough understanding of the biological processes that threaten functional survival of the transplant, that is, rejection and its control. Investigators skilled in immunology, including tissue typing and the management of immunosuppressive procedures, should be readily available as collaborators in the transplantation effort.

2. As in any other scientific investigation, the overall plan of study should be carefully recorded in advance and arrangements made to continue the systematic observations throughout the whole lifetime of the recipient. The conduct of such studies should be within an organized framework of information exchange and analyses. This would permit prompt access by other investigators to the full positive and negative results. Thus the continued care of each recipient would be assured the continuing benefit of the most up-to-date information. Such an organized communication network would also permit the findings to be integrated with the work of others and assist in the planning of further investigative efforts. In this way, it would be possible to insure that progress will be deliberate, and that the experience from each individual case will make its full contribution to the planning of the next.

3. As the procedure is a scientific investigation and not as yet an accepted form of therapy, the primary justification for this activity in respect to both the donor and recipient is that from the study will come new knowledge of benefit to others in our society. The ethical issues involved in the selection of donor and recipient are a part of the whole complex question of the ethics of human experimentation. This extremely sensitive and complicated subject is now under intensive study by a number of well-qualified groups in this country and abroad. Pending the further development of ethical guidelines, it behooves each institution in which a cardiac transplantation is to be conducted to assure itself that it has protected the interests of all parties involved to be fullest possible extent.

Rigid safeguards should be developed with respect to the selection of prospective donors and the selection of prospective recipients. An independent group of expert, mature physicians—none of whom is directly engaged in the transplantation effort—should examine the prospective donor. They should agree and record their unanimous opinion as to the donor's acceptability on the basis of the evidence of crucial and irreversible bodily damage and imminent death. Similarly the prospective recipient should be examined by an independent group of competent physicians and clinical scientists including a cardiologist and an expert in immunology. In this instance the consulting group should also record their opinion as to the acceptability of the recipient for transplantation on the basis of all the evidence including the presence of far-advanced, irreversible cardiac damage and the likelihood of benefit from the procedure.

Enumeration of the above criteria is based on the conviction that in order to obtain the scientific information necessary for the next phase in this form of organ transplantation, only a relatively small number of careful investigations involving cardiac transplantation need be done at this time. Therefore, the Board strongly urges that institutions, even though well-equipped from the standpoint of surgical expertise and facilities but without specific capabilities to conduct the whole range of scientific observations involved in the total study, resist the temptation to approve the performance of the surgical procedure until there has been an opportunity for the total situation to be clarified by intensive and closely integrated study.

Members of the Board on Medicine, National Academy of Sciences

Walsh McDermott (Chairman), Livingston Farrand Professor of Public Health and chairman of the department of public health, Cornell University Medical College, New York City; George Beadle, president of The University of Chicago; Ivan L. Bennett, Deputy Director, Office of Science and Technology, Washington, D.C.; Charles G. Child, 3d, professor of surgery and chairman of the department, University of Michigan Medical School, Ann Arbor, Mich.; Julius H. Comroe, Jr., director, Cardiovascular Research Institute, San Francisco Medical Center, University of California, San Francisco; John T. Dunlop, professor of economics, Littauer Center, Harvard University, Cambridge, Mass.; Rashi Fein, senior staff, The Brookings Institution, Washington, D.C.; Robert J. Glaser, vice president for medical affairs and dean of the School of Medicine, Stanford University School of Medicine, Palo Alto, Calif.; Mrs. Lucile Petry Leone, College of Nursing, Texas Woman's University, Houston, Tex.; Irving London, chairman, department of medicine, Albert Einstein College of Medicine, Yeshiva University, Bronx, N.Y.; Colin M. MacLeod, vice president for medical affairs, The Commonwealth Fund, New York, N.Y.; Samuel M. Nabrit, executive director, The Southern Fellowships Fund, Atlanta, Ga.; Irvine H. Page, Research Division, Cleveland Clinic, Cleveland, Ohio; Henry W. Riecken, vice president, Social Science Research Council, Washington, D.C.; Walter A. Rosenblith, professor of communications biophysics, center for communication sciences, Massachusetts Institute of Technology, Cambridge, Mass.; Ernest W. Saward, medical director, The Permanente Clinic, Portland, Oreg.; James A. Shannon, director, National Institutes of Health, Bethesda, Md.; Eugene A. Stead, Jr., Professor of Medicine, Duke University Medical Center, Durham, N.C.; Dwight L. Wilbur, president-elect, American Medical Association, San Francisco, Calif.; Bryan Williams, M.D., Dallas, Tex.; Adam Yarmolinsky, professor of law, Harvard University, Cambridge, Mass.; Alonzo S. Yerby, professor of public health and head, Department of Health Services Administration, Harvard University School of Public Health, Boston, Mass.

[U.S. Government Memorandum]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
*January 9, 1968.*

To: The Surgeon General.
From: Director, NIH.
Subject: Report for week ending January 5, 1968.

RESEARCH DEVELOPMENTS

SUCCESSFUL LIVER TRANSPLANTS IN FOUR PATIENTS

A grantee of the National Institute of Arthritis and Metabolic Diseases (NIAMD) has successfully transplanted livers in four young girls, all of whom were alive and reasonably healthy 3 to 6 months after operation.

Judicious use of an antilymphocyte serum fraction, together with a new organ preservation technique, has permitted successful transplantation of livers in four young girls, all of whom were alive and in relatively good health 3 to 6 months after transplantation. Good liver function has continued long beyond that achieved in earlier transplantation efforts (maximum of 23 days) and, thus, affords promise for the future.

The four patients ranged in age from 13 months to 2 years and were suffering from disorders which usually are fatal: three, from biliary atresia, a congenital absence of bile ducts; and one, from liver cancer. Donor livers were obtained from four young victims of trauma who otherwise had normal hepatic function.

The scientists described a hyperbaric storage technique which permitted preservation of donor organs for as long as 5 hours before revascularization, thus providing the extra time needed for tissue typing, organ examination, and preparation of the recipient.

Heterologous antilymphocyte globulin (ALG), obtained by fractionating equine antilymphocyte serum, was used as an adjuvant immunosuppressive drug together with azathioprine and prednisone. ALG was administered daily for the first 2 postoperative weeks and was given subsequently every third day. This procedure permitted a reduction of the usual dosages of azathioprine and prednisone and seemed to decrease the incidence of septic complications.

Postoperative difficulties were limited mainly to late development of infected liver infarctions, which were promptly excised or debrided, following which evidence of liver regeneration was noted. NIAMD grantee, Dr. T. E. Starzl of the University of Colorado and associates will report their findings in a forthcoming issue of Surgery.

Mr. FLOOD. I have also before me a newspaper article from the Washington Star. The headline is "Three Heart Specialists Ask Moratorium on Transplants."

I also have before me an item from a paper in my district, the Hazleton Standard-Speaker of Friday, February 9, 1968, and the headline is "Murder Charge Possibility in Transplant Cases Spurs Move To Establish Guidelines." This is an AP story emanating from Los Angeles, which sets forth a series of interesting questions. If there is no objection, I would like to include this.

(The documents referred to follow:)

MURDER CHARGE POSSIBILITY IN TRANSPLANT CASES SPURS MOVE TO ESTABLISH GUIDELINES

LOS ANGELES.—"Any day now—perhaps tomorrow—someone is going to hurl a charge of murder at the doctor in some heart-transplanted case."

This prophecy of District Attorney Evelle J. Younger will lead this week to formation of a committee of medical and legal authorities to draft legislation expected to serve as a guide to cities across the Nation.

The committee, which Younger believes will be the first of its kind anywhere, holds its initial meeting Friday. Younger says it will include representatives from medical schools and societies as well as law-enforcement experts.

"The need is immediate," Younger said in an interview explaining his plan. "I have information that at least two major medical institutions in this area—which I am not free to name—are gearing up for heart transplants whenever the opportunity arises.

"These are reputable institutions, but even they may be subjected to criticism. And what of the small hospital, or the individual doctor, who may have plans that I don't know about? Is there anything to prevent them from attempting a transplant of a heart or some other vital organ? Even if such an operation were successful, the situation is loaded with potential complaints.

"There are many foreseeable situations not covered by existing law. We have a duty to protect the physician from charges that he is using humans for guinea pigs, and at the same time the public must be assured that living beings, no matter how desperately ill, will not be sacrificed.

"The publicity about recent heart transplants is a heady wine. It builds reputations for doctors, hospitals, and even nations."

"South Africa," Younger said, "has never had so much publicity as it has had since Dr. Christian Barnard made the first human heart transplant."

Younger said it is inevitable "that somebody will get in a hurry and use bad judgment as the frequency of such operations increases. We have a duty to anticipate such problems and know how to handle them when they arise."

Among the questions Younger will ask the committee to tackle:

1. Precisely when does death occur? When breathing stops? When the heart stops? When an electroencephalogram shows no further brain activity?
2. Who shall have priority in obtaining available hearts?
3. Who shall give consent for the taking of a heart? Younger pointed out that the donor may be unconscious and unable to give consent, and that relatives—particularly if they are of divided religious beliefs—may seek criminal action later against the physician.
4. Who shall give consent for implanting a heart in a minor?
5. Who may attempt transplants?

Mr. FLOOD. I also have an editorial entitled "Affairs of the Heart," which I think should be included. This approaches it from an editorial point of view rather than straight reporting.

(The document referred to follows:)

AFFAIRS OF THE HEART

The country is learning that the donation of a heart is an extremely complicated business. In Stamford, Conn., it appeared that an excellent heart would soon be available and machinery was set in motion to have the heart transplanted by Dr. Adrian Kantrowitz at Maimonides Hospital in Brooklyn. But the law (and perhaps in part the absence of law) has been invoked to stop it.

The heart belongs to a truck driver with a bullet in his brain, who is said to have no chance for recovery. His wife had magnanimously given his heart to save another life. But Connecticut medical authorities refused to allow the wounded truck driver to be taken to Brooklyn so that his heart could be removed immediately after death occurs. They insist on retaining the shooting victim in the State so that evidence of his death will be at hand and murder charges can be filed.

Further complications arose when the sister and mother of the dying man lodged protests against the proposed transplant operation. So we have a new series of questions added to the many that have already been posed by the sudden escalation of organ transplantation. Does a wife have a right to give the heart of a dying husband? Can such a decision be legally canceled by the unconscious donor's mother or other relative? If the victim of an accident or an assault is conscious, should he be consulted about the disposition of his heart or other organs in the event of death, thus risking anguish that he otherwise might be spared?

In Maimonides Hospital two patients in peril of death were hoping for the truck driver's heart. One was a young woman and the other a man in his fifties. How should the decision be made? Are hearts to be purchasable? If not, should the only heart available go to the sickest patient or to the one with the best chance for recovery? To what extent should youth be preferred over age? Should the potential usefulness of the individual recipient to society be controlling? If so, on what basis should the judgment as to potential usefulness be based?

Questions are also certain to arise as to whether the State has a right to donate the heart of a convict who dies in prison without known relatives. And will a man who has little or no chance to live be allowed to sell his organs as spare parts for the benefit of his family?

If the transplanting of hearts becomes a general practice, no doubt many individuals will voluntarily give the right to use their organs for others in the event of a fatal accident or death from other causes. And it should not be difficult to satisfy the demands of the law for evidence in cases like that at Stamford. Nevertheless, it is evident that the world has entered upon a new epoch in medicine that will have far-reaching ramifications in law, ethics, medical practice, and human relations. The perfection of a good mechanical heart has become vastly more urgent.

Mr. FLOOD. I also have before me a column of the Evening Star, December 13, 1967. It is Max Lerner's column and the headline is "Does Transplanted Heart Mean New Person?"

We will put that in because these are interesting reading on the subject.

(The document referred to follows:)

DOES TRANSPLANTED HEART MEAN NEW PERSON?

(By Max Lerner)

The Capetown heart transplant has not only sent a shiver of excitement around the world, but has raised gritty questions about the nature of life and death and the margin between them. I shall not repeat here what is being widely discussed about the surgical breakthrough itself and reverses that may still occur through the body's rejection of the transplanted heart. Instead I shall assume that the tide of surgical technology will move on and that Capetown is only a beginning. The real questions turn on what it means.

We used to be fairly clear that when the heart stops beating and the brain stops functioning a man is dead, and the whole complex organization we call a human personality is no more. Then came the cases where the heart was revived, and with them the nagging question arose: What shall we call the man during that interval? Was he still alive, even without a heartbeat? Or was he Lazarus, who died and then came back from the dead? Was there a personality without a functioning heart?

I think we shall have to say that a man is alive and is a person so long as his vital organs—heart and brain—have not stopped for good; so long as their stopping, for whatever reason, has not been shown to be irreversible. Similarly, as in the Capetown case, a man is alive even when his heart has been cut out of him and while his body is waiting for the heart of another to be inserted where his own had been.

The real conceptual difficulties come up after the heart has been put in place. Who exactly is Louis Washkansky now? Is he the person whom his wife and friends knew as a 55-year-old grocer with a worn-out fibrous heart? Or, now that the heart of Danise Darvall is in him, is he a new entity that combines both of the former people?

If the latter is true, it raises in a new form the old question of immortality. Not in the sense of life forever, but at least in the sense of a span of life beyond the allotted life of one's body. For in the Louis Washkansky who was well enough last week to take part in a broadcast, and who seems a new man to his family, something that was a crucial part of a 25-year-old girl is now a crucial part of the new life. One may argue that the girl who died is not truly dead, that the man who lives is not the man who lived before. Both the man and the girl, in his view, have formed a new entity, and in a meaningful sense both of them live.

This is, however, relatively simple compared with what will arise when man succeeds in a human brain transplant. It is by no means impossible. Prof. Robert White of the Brain Research Laboratory at the Metropolitan General Hospital in Cleveland has done it with rhesus monkeys and is certain it can be done with human beings. In an interview with the Italian journalist Oriana Fallaci, in a recent issue of Look, he says that it can be done with existing techniques. He predicts that the Japanese will be the first to do it, not himself, because "I have not resolved this dilemma; Is it right?

The earlier peoples—the Mesopotamians, the Egyptians—did not think the brain was a particularly important organ, and the Egyptians didn't even trouble to preserve it with the embalmed bodies of their dead. Yet for us, in the later centuries, it has become the one crucial part of the human being, even more decisive to his personality than the much sung heart, exactly because it carries the total record of experience and, therefore (so Dr. White seems to believe) the soul itself.

If we ever get a successful human brain transplant, will the "new" person know what has been forgotten from the loss of the old brain, what new things are remembered from the gain of the new one, what difference in thinking and character the change has made? Simply to put that question is to understand why Dr. White shrinks from the hubris of tampering with a brain transplant. Yet if we don't attempt it, how shall we ever know whether his scruples have a base?

Mr. FLOOD. Is there anything at this point you would wish to add to this?

Dr. SHANNON. Very briefly. Organ transplantation is still in the very early stages of investigation. It should be undertaken only after careful consideration and only in those situations where you have the most complete control possible over the patient. These operative procedures should be done serially rather than in parallel. This is a time when progress, to be effective, must be as a result of very cautious, careful, thoughtful work.

We are taking the comments of the Board on Medicine of the National Academy of Sciences and modifying them so that we can incorporate them into the general guidelines we have for clinical investigation by grantees whom we support.

I think the Board on Medicine came up with a very thoughtful statement. I think, in our frame of reference, we will probably limit ourselves, in the guidelines we issue to very broad general principles that are amenable to incorporation in control devices that are already in existence in the institutions where NIH supports work.

Mr. FLOOD. At this luncheon that Senator Hill gave for the South African, Dr. Barnard, I asked Barnard this: "The newspaper stories said that you have 30 people on a team. Now, this kind of team, from the person who presents the anesthesia down to the last person—it is quite a team. Thirty of the best people in that area. And a lot of people think that this shouldn't be permitted."

Doctors tell me, "We do not at this time want a team of hand-picked experts like you being locked up in a room at the end of the hall someplace, where you come out only when somebody has a heart to transplant. The manpower shortage is too great to lose the regular ongoing contributions of such people."

Dr. Barnard said, "This is not true, even with my team. These people work, just as I do. They are trained for this extra work; we have special training and teamwork, but as far as your concern is concerned, this is not so because these people do whatever they were doing at any other time."

Dr. SHANNON. Barnard is correct. Where heart transplant will take place, or has taken place in the past, it is only feasible if there is an already existing, highly sophisticated team of integrated surgeons, nurses, anesthesiologists and immunologists. At this stage, the actual heart transplantation would be a striking exception to normal routine. It would not interfere with these people performing their normal service to the community.

I would like to say that the number of people who could benefit from some type of heart-assist device are so numerous that to attempt to solve

this problem by heart transplantation is probably impossible. You have two courses, really: prevention or amelioration of the progress of the disease or the development of a mechanical device. I think that, meanwhile, heart transplantation should go forward but with the full understanding that it is an investigative procedure, with all the controls both moral, ethical, biological, medical, and support systems——

Mr. FLOOD. Now, I am speaking of transplants generally; not just the heart. Does this apply to body organ transplants generally? That is what I am talking about.

Dr. SHANNON. The Board on Medicine's statement makes a sharp differentiation between what is called single-organ transplantation and kidney transplantation. Now, if you transplant a kidney, you are dealing with one of two organs. The donor is still left with a good organ. If the recipient rejects the kidney, you can carry him with something else and try again. If you talk about liver or heart, you have single organs. The donor cannot live without it, and the recipient cannot live if he rejects it as there is no way of carrying him.

Mr. FLOOD. You are aware that this thing is being discussed by everybody?

Dr. SHANNON. Indeed, I am.

Mr. NATCHER. In heart transplant cases, does the heart that is removed from the donor have to be beating?

Dr. SHANNON. No, sir; it doesn't have to be beating, but it cannot be left unprofused by blood for very long before it is removed from the donor. The problem, Mr. Natcher, is that with our ability to give artificial respiration, and to assist the circulation with mechanical devices and the like, the time of death is less easily determinable now. At the present time several of the States are attempting to enact laws which will define death in terms of cerebral activity which is measurable by electrical current. You can drive a heart with a pacemaker long after the patient is dead by all other criteria. You can respire the individual with forced respiration. You can maintain some circulation through the use of drugs, even though cerebral activity is totally gone, and by all other criteria the patient is dead. This is the difficulty.

That Board's statement points out that the surgeon who both takes the heart and implants it is so emotionally involved in what he is doing that he is a poor judge of the criteria that are to be used, either to take or to give.

Mr. FLOOD. Two very distinguished surgeons told me about 2 months ago, when we were discussing this—and this is my language, not theirs, and I don't want to be facetious—but, in effect, I would put it this way: The actual transplant of the heart is no great trick. Any first-class surgeon or team can do that. The real trouble lies in the rejection problem.

Dr. SHANNON. Rejection is the big problem.

## COORDINATION OF BEHAVIORAL SCIENCES

Mr. FLOOD. Mr. Laird?

Mr. LAIRD. Dr. Shannon, the Appropriations Committee, during the past 2 years, has been hearing more and more about the behavioral sciences.

When Dr. Yolles was before the committee, I went into the work that the National Institute of Mental Health is doing in the area of

behavioral sciences. They have had an expanding program in that area for several years.

I first became interested in it when the bill emanating from this subcommittee was attacked on the floor of the House and on the floor of the Senate about 6 years ago. We were funding some research grants that had to do with behavior of monkeys under different situations, the family situation of monkeys, the love of the mother for her children, the reaction of young monkeys whose mother was taken away, and so forth.

Dr. Harlow's project was under rather severe attack in the press because, more than anything else, of the title of the project.

Research in behavioral sciences is becoming more of a factor in the appropriations requests for the 1969 budget, in the Department of Defense, in the National Science Foundation, the Space Agency, the National Institute of Mental Health, and now with NIH.

It so happens the project that was under attack 6 years ago happened to be at the University of Wisconsin and it was directed by Dr. Harry Harlow. I think that project has worked out very well. I recently was at the White House as the President presented one of the National Science awards to Dr. Harlow for his work in this area.

You recently had a review made of the responsibility of the National Institutes of Health in this whole area of behavioral sciences. Your report on the subject proposes to place special emphasis on the behavioral sciences in the next 5 years, with the National Institute of General Medical Sciences, the National Institute of Child Health and Human Development, and the National Institute of Neurological Diseases and Blindness. It recommends a $5 million increase each year in these three institutes in the area of the behavioral sciences.

Do you think there is sufficient coordination and supervision Government-wide in this whole area of research investigation in the behavioral sciences?

Dr. SHANNON. I think that I can answer that question in two parts. I think that there is adequate supervision, integration, coordination in the programs of the Public Health Service.

COORDINATION OF ALL FEDERAL RESEARCH IN THE BEHAVIORAL SCIENCES

I think there is awareness on the part of the major elements—NASA, National Science Foundation, DOD, Public Health Service. There is awareness of the major thrust of each of these other programs, but I cannot in conscience say that I believe that there is detailed awareness to the extent that it is adequate for future programing of work in the behavioral sciences without one agency vying with the other over the content of the programs.

There are mechanisms within Government whereby this can be done. I would not propose that these mechanisms be thrown into action at the present time because the other agencies, even as ours, will not have funds in the immediate future, to implement the plans that they have for these areas. I do not see so rapid a growth that it will cause overlap and conflict rather than coordinated advances.

A mechanism that can be used, and has been used very effectively in the past, is that the Office of Science and Technology, a part of the President's Office, advises the agencies and the Bureau of the Budget,

as the budget process evolves, to insure that suitable emphasis is given to an area in science—in this case the behavioral sciences—by the agency that the Office of the President has elected to play the major role in this development. I think that our intent would be to send the report that you saw on behavioral sciences, which was prepared for our own guidance, to the Office of Science and Technology for such purposes as they saw fit to use it for in developing such a coordinated approach.

Indeed, that report has already been sent to the Office of Science and Technology for their information.

MANAGEMENT TECHNIQUES OF EXTRAMURAL RESEARCH PROGRAMS

Mr. LAIRD. Dr. Shannon, in this report which I had an opportunity to go over last night, there were several new approaches to the administration and management of various extramural programs. Would you outline a few of those new approaches in administration and management in the area of behavioral science research grants, and other research activities?

Dr. SHANNON. The major management device is really the device that we already use, namely, the allocation of grants among institutes. The second is to develop significant training competence and then to expand support of that area so that, research support is made available in parallel, in adequate fashion to make full use of the environment.

I believe the third is to provide adequate resources both for the members of the community who are supported and those who are operating in parallel fields. We really use these management devices at the present time. If that does not answer your question, Mr. Laird, maybe I don't quite understand its import.

Mr. LAIRD. What I was concerned about was whether there was any real management program not only applying to the Institutes for which you have responsibility as Director of NIH but to the various governmental programs that are carried on in other agencies. Look at the expansion in the Space Agency, Department of Defense, and the National Science Foundation over the last 5 years in this area. It is perhaps the largest percentage increase of any area of research that is being carried on in the Government.

I include in that even the weapons research that is being carried on in the Department of Defense and in these other areas of R. & D. in the Defense Department.

I was interested in finding out what kind of management techniques were being used by the executive branch. Your report deals with the management techniques of NIH. It does not deal at all with Government-wide management techniques in this very important area where we have the highest percentage of any increase in research activities of the Federal Government.

Dr. SHANNON. That report that you saw made use of a central pool of information from the Science Information Exchange that covers all work supported in the area, by all Government agencies. It was prepared with an awareness of everything that was going on at that time, although it only dealt with our own internal problems.

As I said earlier, though, I do not believe that there is adequate central coordination for all the agencies that would like to do it, given a 5-year period of operation in this area. I do not think that has been a problem up to the present time because, although the percentage increase has been very high, the absolute sums involved are quite low. The field is characterized more by deficiencies of support, wherever you look, than by overabundance of support.

If the plans of the various agencies that impinge on the problem were in fact to come into play, then I think the absence of central management devices would be very bad. Some of us believe that, not only in this field but in other fields, our central management of science is somewhat deficient—when one views the activity across the board—both in terms of the executive agencies that perform or support the science, and in terms of the congressional committees that must act on their proposals.

We have suggested to the President's Science Advisory Committee, the Office of Science and Technology, and indeed the Secretary of HEW, that perhaps the time has come to establish, quite formally, cognizant agencies over broad areas of science, so that both the executive branch, on the one hand, and congressional committees, on the other, could look to one focal point for data on the area, for analyses, and, perhaps, for general recommendations as to the adequacy or inadequacy of support.

Such cognizance does not exist, and it is my belief that the Office of Science and Technology is not adequately staffed to take on this very large burden. I think it is probably not desirable that they should. The establishment of a cognizant agency to supply information on research, rather than to direct the total research effort, should, I think, be acceptable to most executive departments.

Although we do not have such a series of cognizant agencies now, this will almost certainly be required in the near future. Let me be specific.

I trust that this—and I want this on the record, Mr. Laird—I trust that other agencies that impinge on our activities will not feel that I am presumptuous, but I believe that NIH exerts such a dominant influence on the biomedical sciences that it would be the logical one to be asked to serve as the cognizant agency in the biomedical sciences.

I think it would not be inappropriate to designate the National Science Foundation to be the cognizant agency in the physical sciences, mathematics, and engineering.

I think it might be appropriate to designate the new foundation that has been proposed by Senator Harris, or the Office of Education, one or the other, to be the cognizant agency for behavioral and social research.

One might wish in order to provide balance to develop a fourth area that would deal with the noninvestigative aspects of higher education. There would be little point in setting up these cognizant agencies without also establishing on a very high level in the Government—perhaps at the level of the Council of Economic Advisers, the National Security Agency, or the like—some board that would concern itself with the development of national goals and national priorities; that would be able to assess, with the information given it by

these cognizant agencies, whether the Nation was indeed making suitable progress toward these goals; and that would also concern itself with institutions of higher education, generally, not only with research and development institutions and industries, but with the mix of research, development, and education. This was certainly part of the concept when the National Science Foundation was first discussed.

This function has never come into being nor is it likely to come into being with our present structure.

I realize that this proposal encroaches somewhat on some of the authorities of the present National Science Foundation, some authorities of the present Office of Science and Technology, and some of the authorities of the present Science Advisory Committee.

In the aggregate, the function of the setting of goals for science, technology, and education; assessing progress toward these goals; determining whether, indeed, it is in the national interest to do this or that in terms of very broad priorities, could well be the most important single thing to which we should address ourselves.

### BEHAVIORAL STUDIES OF EMPLOYEES

Mr. LAIRD. Dr. Shannon, starting, I believe, with the 1967 budget, several of our departments, for the first time we saw funding of behavioral studies of employees. We also note that in industry a great deal of behavioral study is being done of employees not only prior to the time they are hired for certain jobs but also in connection with advancement.

What concerns me, however, is that I am not always certain these people are qualified to carry on this kind of work. I wonder whether we have developed the people that can make the kinds of determinations that are being made not only by personnel departments in government, but also by personnel departments in industry?

Dr. SHANNON. Mr. Laird, this is an outgrowth of what actually began during World War II in what was called psychological guidance or, if you will, employment practices. I am not an expert on this.

Mr. LAIRD. Is anybody an expert on this? I am beginning to wonder sometimes. This seems to be the thing to do now.

Dr. SHANNON. Mr. Laird, we have not felt that the devices are sufficiently sophisticated and sufficiently determinable for us to use them in our operation. Perhaps I can answer you on that basis.

Mr. LAIRD. I think that is a pretty good answer.

### MONGOLISM

Dr. Shannon, there has been rapid progress, as you noted earlier in the presentation, in the whole area of biomedical knowledge. What progress has been made in the area of mongolism?

Dr. SHANNON. The only thing that has happened in mongolism, to the present time, that could be put to use in practical control of mongolism is the observation that it appears to occur in children born late in a marriage rather than early in a marriage. This is a poor control device. It is a genetically transmitted disability and it is characterized by defective makeup of the full compliment of genes. We

have no way of influencing that in a direct way at the present time. Some of the very recent work on the information system by which cells transmit genetic information from generation to generation and the characteristics of the nucleic acids that control that information, suggests that, perhaps sometime in the future, it may be possible to substitute genetic material for defective genetic material or remove excess genetic material by chemical means.

This is not available now nor will it be available in the foreseeable future.

## Compensation System at NIH

Mr. Laird. Dr. Shannon, for the last several years I have discussed with you the experience of NIH as to the loss of personnel, and the effect of the salary situation. You do not have the authority to use the authorization which the Armed Forces now possess to pay dual compensation to commissioned officers; do you?

Dr. Shannon. We do under certain circumstances, Mr. Laird.

Mr. Laird. What are those circumstances?

### DUAL COMPENSATION

Dr. Shannon. Our ability to use dual compensation is limited to commissioned officers under circumstances precisely analogous to those set down by the Department of Defense. The problem is that the requirements of the Department of Defense for the use of that basic legislation are quite different from ours.

Mr. Flood. Would you, for the record, define dual compensation?

Dr. Shannon. Yes, sir.

Dual compensation is a device, under a law passed some 2 years ago, which permits a commissioned officer to retire after 20 years of service and to be reemployed by the Government without a total loss of retirement pay though he receives his full civil service pay for the job he is employed to do.

I do not recall how much of his retirement pay he may retain.

Mr. Laird. Supply that for the record.

Dr. Shannon. Yes, sir.

(The information follows:)

### Dual Compensation

As originally enacted, the Dual Compensation Act of 1964 (Public Law 88-448) provided that a retired officer of any Regular component employed in a Federal civilian position shall receive, in addition to the full pay of the civilian position, retired pay while so employed at an annual rate equal to the first $2,000 of his retired pay plus one-half of the remainder. The $2,000 base has been increased since then to $2,074, taking into account adjustments in retired pay to reflect changes in the U.S. Consumer Price Index.

Dr. Shannon. We have had, in our own Department, what I believe to be too narrow an interpretation of the law, especially as we have a very large number of commissioned officers able to take advantage of this new legislation. This is unfortunate in the face of devastating losses of senior personnel, particularly in some of the Institutes.

Mr. Laird. Some of these people leaving are young people in their most productive years. They have quite a few years during which they could still make a considerable contribution.

Dr. SHANNON. Yes, sir. It is particularly bad at the present time. Let me say what continuation pay is now and then I will continue with the other.

Continuation pay, depending on the years' service is given to an individual who commits himself for an additional period of service. I might say this is limited to medical officers in the Commissioned Corps. The individual gets a bonus for continued service. In the case of an officer who has 14 years or more service, this is a substantial sum.

The unfortunate thing is that scientists and engineers do not get incentive pay which a medical officer gets at the rate of $350 a month. He does not have continuation pay available which can be as high as $5,200 a year for a medical officer. That would be something more than $400 a month. The result is that the science officer or the engineer officer may be working side by side with a medical officer and the pay differential between these two people could be more than $9,000.

In those situations, we would like to take advantage to the hilt of dual compensation, where the law permits, because, while not many people are in this situation, the few that would benefit from the use of this technique are terribly important to us.

While continuation pay provides the medical officer with about 20 years' service an additional $5,000 a year—and this constitutes a substantial increase in income—it is important to realize that, it in no way, influences his ultimate retirement benefits which still relate to base pay. So that although the continuation pay will add to income during the current year, it does not prepare that individual for his later years. The use of dual compensation, on the other hand, would not give him much more in the way of take-home pay at the time but it would increase the base from which his retirement is calculated by somewhere between $8,000 and $10,000 a year.

He would have to serve under this dual compensation for some 5 years before he gets the full benefit of it. Thus it would become operative at the very time when we are losing our most important people, that is commissioned officers in the 20- to 25-year period. This is the period when they are the greatest use to us. Theoretically, the Surgeon General does not have to permit such an officer to retire. But, Mr. Laird, a dissatisfied professional who feels an injustice has been done is not a very effective worker.

We are in a peculiar position on this 20-year retirement. It has been used by us as an incentive for an officer to stay 20 years, and then, if we restrict his retirement, we are not being honest with the individual because the incentive is removed at the time he elects to take the option. My own belief is that this problem of pay, or this problem of inadequate pay in organizations such as the National Institutes of Health, really carries in it the seed of destruction of the organization.

You have heard me say this before, Mr. Laird. I think that beyond any doubt we have an organization which is at least equivalent to any scientific organization in the world in terms of competence and productivity. It is equally certain in my mind that unless we can find some way of bringing the compensation of these very superior scientists up to the level of the compensation that they can get in medical schools, universities and industry, our losses will be too great

for us to find replacements from among the younger scientists we have trained.

We find great difficulty in getting exchange at the top. Essentially, we have very little ability to attract senior people. We feel that our organization will only continue to be an alert, vibrant, viable organization if we have exchange with the universities and the industrial world at all levels.

We feel that in those Federal agencies that are so-called old-line agencies—where the laboratories look a little tired and lack the innovative spirit and dynamism that we feel characterizes our agency—we feel this is because they have not provided for a broad exchange at all levels so that the agency's laboratory can be a part of the entire scientific community rather than a segregated area that becomes ingrown.

LOSS OF PERSONNEL

Mr. LAIRD. What is the experience on the loss of personnel at NIH? We discussed this at some length a few years ago. What is the experience now?

Dr. SHANNON. Dr. Fredrickson, the Director of the Heart Institute is leaving his position. Dr. Masland, Director of Neurology and Blindness, is leaving his position. Dr. Fredrickson is going to stay at NIH but wants to return to active research. Dr. Masland is going to P. & S. I expect, without naming them, that two more directors will leave us within a 2-year or, at most, a 3-year period.

Let me take the Heart Institute as an example. Dr. Mider is moving over to a less physically taxing job in the National Library of Medicine about the 1st of June. He is being replaced by Dr. Berliner who is now Scientific Director of the Heart Institute. We are thus taking the Scientific Director out and also moving the Institute Director.

At the same time, Dr. Steinberg, who is Chief of the Laboratory of Metabolism, is moving to the University of California, San Diego. Dr. Braunwald, who is Clinical Director and Chief of the Cardiology Branch, is moving to the University of California. Dr. Udenfriend, who is Chief of the Laboratory of Clinical Biochemistry, is going to industry to head up a new research institute at Hoffman LaRoche.

You cannot take an institute of that size and lose that many people. This is all in a 6-month period, and all of these people are taking some of their second-line people with them. There has to be now at this late stage, a total rebuilding of that intramural research program. I do not say that we would not have lost some of these people anyway and we should be prepared to replace some of them from within. In point of fact, if we cannot train research people who are as good or better than those trained at the university, then I do not think we are doing our job.

At the same time, we are losing too many people at this level for a viable organization. I think that scientists should move primarily because of scientific opportunity. They should not move because they cannot afford to educate their children. This is why we are losing some of our people.

By using dual compensation and continuation pay, it will be our purpose to try to get relaxation within the law, to the extent possible,

to make use of every device that we possibly can to increase the salaries of people in this critical category.

### HEALTH PROFESSIONS PERSONNEL BILL

Dr. STEWART. Mr. Laird, the administration has submitted a bill to Congress this year for a new personnel system in the Department. It will take care of some of the inequities that Dr. Shannon mentioned, particularly the retirement system, incentive pay, and continuation pay problems in the commissioned corps of the Public Health Service. It cannot solve the immediate problem until it becomes law and it does not solve the problem of comparability of pay that Dr. Shannon is talking about. It does take care of some of the inequities that are in the system.

### FEDERAL AID TO INSTITUTIONS COMPETING FOR FEDERAL PERSONNEL

Mr. LAIRD. Four years ago I discussed with you the problem that we had of really financing our own competition. I am not referring to that in a flippant way. I do think there is a point to be considered here.

Through our grant programs to the medical schools and to the industries under contract, not only with money in the HEW bill but in some of the other bills. We are spending some $15 billion in the area of research and development.

Do you think we are financing our own competition and putting ourselves in this difficult position?

Dr. SHANNON. The answer to that is "Yes," but I would not like to make it so simple. At the beginning of the development of the Federal programs for research and development, the scientists, particularly those in universities as well as those in Federal establishments, were grossly underpaid. I think the infusion of large amounts of research and development dollars has relieved that until, at the present time, scientists, wherever they may be—except inside of government—are now being very adequately paid for their professional services. It may be that some are paid more than they are worth. I cannot make that judgment either generally or specifically.

Mr. LAIRD. In the Department of Defense Subcommittee we finally had to take action on some of the dummy corporations that were set up. We did this in our Defense appropriation bill because these corporations were being set up as "think shops" with a quasi-public corporation structure. Sometimes they even doubled salaries that were being paid on the Government payroll.

We had an investigative report and we finally had to establish salary limitations. I don't like to do that, but I wonder if we shouldn't look into that once again.

Dr. SHANNON. Mr. Laird, we do not have that type of support program. I have read those reports and read those hearings. I think that the control of salaries in what are the equivalent of wholly owned corporations is relatively simple as contrasted to an attempt on our part to regulate academic salaries.

I think that it would be most inappropriate for us to attempt to influence salary systems in universities across the Nation. Basically, I am less concerned with our inability to compete with industry, where

salaries are substantially higher, than I am with our inability to compete with the best university science departments.

Mr. LAIRD. In your discussion here and your outline of the situation facing the National Heart Institute, we have revealed quite an alarming situation, as far as I am concerned. In one year this important Institute really can be gutted of its top management personnel.

DEPARTMENT POSITION ON NIH COMPENSATION SYSTEM

Mr. KELLY. Mr. Laird, I wonder if I might comment on the departmental aspects of a couple of the questions that you raised. On the one, I agree with Dr. Stewart, in the long term we are trying to make some approaches that will grant, we hope, some relief. The new health professionals personnel bill that has been recommended to the Congress is one such approach.

The second is that the Congress has enacted a methodology for lifting the ceiling of the executive pay bill. This ceiling on the executive pay scale adversely affects the problem of comparability pay at all levels below it. It places a ceiling of $28,000 on the pay of any position not in the executive pay bill. A year from today this should be lifted and should give some relief with respect to the question. In the interim period we are conducting a reexamination of the dual compensation provision. Dr. Lee has initiated discussions at the Office of the Secretray level including the Assistant Secretary for Administration and myself. We hope to have conversations with Dr. Shannon and Dr. Stewart leading ultimately to the presentation of a policy to the Acting Secretary in order to deal with this problem in the interim period pending the lifting of the ceiling of the executive pay bill.

I also would like to underscore what Dr. Shannon has said with respect to our salary policy. We are alert to the problem that you raise. We are examining those places where the HEW or the Federal Government are participating in Federal support of programs that are predominantly Federal funds and where it is predominantly or entirely HEW funds.

We do think it is appropriate we review individual salaries. We are asking that those cases where the salary is in excess of $25,000, that each such case be reviewed on its merits. We are not setting a ceiling. We are just asking that a judgment be exercised.

These are relatively few cases. The preponderance of our activity supports the conduct of effort carried on in institutions where the Federal Government is not the predominant source of funds.

Our policy has been, and we would urge that it continue, that we pay the salary level that the institution arrives at as its personnel policy and practice; that the method by which they administer their own funds be the method that they use for the administration of Federal funds, that they cannot pay people a greater salary because they are being supported by Federal funds, but they are under no necessity to pay them a lesser salary. Grantee institutions apply their own personnel policies on the programs supported by HEW. We think this is a sound and a basic policy of a concept of a partnership arrangement which these grant-supported programs are designed to carry out.

PUBLIC HEALTH SERVICE REORGANIZATION

Mr. LAIRD. Dr. Shannon, late in November and in early December I had an opportunity to visit with former Secretary Gardner at some length about the reorganization plans of the Public Health Service. We discussed particularly the plans as they affected NIH and the advisability of joining science and education activities together, particularly NIH with the Bureau of Health Manpower.

In the proposed plan, after much consideration I know that the Secretary took the position, and I think this was concurred in by Dr. Stewart and others after quite a little discussion, that the manpower activities would be transferred to NIH. Is that correct?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. This plan has not gone into effect as yet, but I assume that this will be the plan that is finally agreed upon. What elements will be transferred to NIH under this new plan?

Dr. SHANNON. Mr. Laird, at this point I do not know. I can only tell you what our recommendations were.

Mr. LAIRD. What elements can be transferred with profit then?

Dr. SHANNON. It is my conviction that support of science and support of education are intimately intertwined today and that they should be administered by a single organizational entity. At the very least, I think that those elements of support of education and support of manpower that deal with the professional manpower be transferred and be administered in parallel with support of research and support of research training such as is done at NIH today.

Whether it is advisable to transfer all manpower such as paramedical personnel, technicians, nurses, and the like to NIH is a less clear question in my mind.

Secretary Gardner felt that the simplest way was to transfer the entire manpower function to NIH and then, in the course of the subsequent years, to sort out those things that should be held at NIH and those things that could be more beneficially handled by other segments of the Public Health Service or the department.

It may well be that this is the simplest way to do it. The question is primarily whether you consider the key individual in the manpower pool to be the individuals who are called scientists, educators, and practitioners, or whether you develop the system in a more service-oriented way so that you develop medical teams.

With the array of new professionals that will be needed in the coming 5 or 10 years, the important policy decision that has to be made is whether all manpower programs should be joined to the other academic endeavors—such as support of research, support of research training, and the like—or whether only those manpower activities that relate to professional manpower should be transferred.

Mr. LAIRD. What is your recommendation?

Dr. SHANNON. Our recommendation is the one we finally worked out in the Secretary's Office, transfer the entire operation and let us sort it out after the first year.

Mr. LAIRD. What advantage does that have as far as program development?

Dr. SHANNON. The main advantage is that it would give us the ability to go forward with straightforward institutional development. We have authority for health research facility construction, we have construction authority in the Health Professions Educational Assistance Act. We have authority to support institutional activities through general research support grants, we have authority for institution grants in the Health Professions Educational Assistance Act. We have authority to support projects of a developmental nature in each.

If one melds these authorities, one can make effective use, in parallel, of support for research and for graduate education. You can deal, in a single agency, with the total requirements of an institution, and an institution is then in position to discuss its problems at a single point within Government—I am talking about a medical school or the biological elements of a university, dental schools, and so forth. They would have the opportunity to discuss institutional development with one official who has access to a variety of devices that may be needed to develop that institution.

At the present time these authorities are distributed among several operating agencies, decisions are made by several decisionmaking groups—councils and the like—and the mechanics are more costly.

It doesn't always happen that one council is in agreement with the other. You may get split decisions and this is distressing to facility administrators, to manpower administrators, and certainly to the institution which, in the final analysis, is the point of growth that we are attempting to encourage.

The present system does not tend to clean administration and does not tend to facilitate real planning at the institutional level.

### SCIENCE OPPORTUNITIES

Mr. LAIRD. Dr. Shannon, in your statement, and in the discussion, we have heard referred to 30 or so areas that need more rapid development, the so-called science opportunities. I wonder if you could describe these areas for the record and supply us a brief description of each together with—and I will underline this—a conservative figure for the dollars needed for the growth of these programs as we go down the road for the next few years.

Dr. SHANNON. I would be glad to do this, Mr. Laird. We have just completed an in-depth review, program by program, in anticipation of the development of the 1970 budget and in anticipation of the 5-year projections for the program planning and budgeting system. The program areas I alluded to in my opening statement have been isolated, have been studied, and have been discussed—without regard to the present financial restraint—simply from the standpoint of where they should go in the 5-year period. We will be glad to furnish this for the record.

(The information requested follows:)

National Cancer Institute

The Cancer Therapy Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct Operations: | | | | | | | | |
| In-House..... | $4,196 | $4,400 | $4,450 | $5,302 | $5,854 | $6,505 | $7,135 | $7,819 |
| Contracts..... | 20,234 | 20,650 | 20,665 | 23,512 | 26,660 | 30,016 | 33,688 | 37,684 |
| Total | 24,430 | 25,050 | 25,115 | 28,814 | 32,514 | 36,521 | 40,823 | 45,503 |
| Related grants..... | 4,343 | 4,343 | xx | xx | xx | xx | xx | xx |
| No. of positions.... | 352 | 375 | 375 | 415 | 434 | 454 | 474 | 495 |

The objective of the Cancer Therapy Program is to select from the millions of available chemicals those materials that will cure one or more of the hundreds of human diseases called cancer and to discover the best way to administer these drugs to control both fast and slow-growing tumors. Recent advances have shown a sharp difference in drug control of fast-growing tumors as contrasted to slow-growing tumors. Drugs used intensively and in combination exert virtually complete control over some far advanced, fast-growing tumors, with consequent long-term survival and probable cure. Research into the reasons why not all fast-growing tumors are controlled has led to new clues to the biologic differences between fast and slow-growing tumors. The major impediments to achieving further advancement lie in the clinical area. Cancer Therapy Program increases for Fiscal Year 1970 are considered to be of the highest priority and consist of 30 positions and $500,000 for the Baltimore Cancer Research Center and the Clinical Center at Bethesda, Md., and 2 positions and $1,440,000 to establish a major clinical contract effort. These positions and dollars will be devoted to the clinical application of the significant breakthroughs gained in the fast-growing tumors to attack the more prevalent common slow-growing tumors, such as cancers of the lung, breast, and colon.

The principles established for control of fast-growing tumors require improvement of several existing clinical units in order to study intensively and in the highly individualized fashion needed patients with non-responsive fast-growing tumors and with cancers of the lung, breast, and colon. These intensive units must have teams trained in chemotherapy and radiation therapy; ability to replace platelets and granulocytes and to provide a protected environment; and research back-up in chemical pharmacology and cell-cycle kinetics.

During Fiscal Year 1969, NCI intends to start three such units at a low level of activity. These should rapidly enlarge over the next few years and one or two new units should be added each year. Since the natural history of the slow-growing tumors covers 5 to 10 years, the program should be accelerated in order to avoid delay of judgment on the importance and pertinence of the new principles involved.

National Cancer Institute

The Third National Cancer Survey
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| In-House..... | -- | $25 | $55 | $554 | $808 | $862 | $602 | $472 |
| Contracts..... | -- | 85 | 250 | 1,273 | 1,437 | 1,157 | 678 | 401 |
| Total | -- | 110 | 305 | 1,827 | 2,245 | 2,019 | 1,280 | 873 |
| No. of positions.... | 0 | 2 | 5 | 37 | 47 | 49 | 43 | 36 |

Cancer is not a reportable disease. While cancer deaths are included in mortality statistics we must rely on special studies to gain information of a more detailed nature and on incidence and prevalence and variations between population groups. It has been twenty years since a nation-wide survey of the extent and impact of cancer in the United States has been undertaken. Two earlier cancer incidence surveys, in 1937 and 1947-48, covered ten large metropolitan areas. A survey in Iowa in 1950 helped provide knowledge of cancer incidence in rural areas. While data from these surveys have provided key baseline information, the data are now out-of-date. Moreover, there has never been a comprehensive survey that was designed to provide reliable data on incidence in relation to such items as occupation, number of children, economic and social factors, etc.

The new survey is planned to cover a three-year period centered around the 1970 census and to include ten large metropolitan areas and two states (Iowa and Utah). The main product will be analysis of incidence rates for the various types of cancers, and reports will be on special problems, such as the relation between occupation, cancer incidence, and the burden of cancer on the economy.

It will provide reliable answers to important questions such as variations in the incidence and prevalence of specific forms of the disease, relationships with other factors, and the economic costs to a community.

A pretest of all aspects of the survey will be conducted in Birmingham, Alabama. The pretest is scheduled for May-July 1968, so that there will be time to analyze the results and make any changes indicated before the main survey begins in January 1969.

The survey will be conducted by in-house staff and a number of contractors. The last survey and analysis took nine years to complete. With extensive use of computer technology, it is anticipated that the first reports for this survey can be completed in five years from the start of the survey (two years after completion).

National Cancer Institute

The Solid Tumor-Virus Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| In-House..... | $1,290 | $1,590 | $1,609 | $2,572 | $2,933 | $3,172 | $3,360 | $3,558 |
| Contracts..... | 3,137 | 3,384 | 3,385 | 7,622 | 10,676 | 12,947 | 14,737 | 16,548 |
| Total | 4,427 | 4,974 | 4,994 | 10,194 | 13,609 | 16,119 | 18,097 | 20,106 |
| Related grants..... | 3,073 | 3,227 | xx | xx | xx | xx | xx | xx |
| No. of positions.... | 88 | 89 | 89 | 131 | 151 | 166 | 176 | 181 |

Recent advances in virus-cancer research, program operational capability and production of several critical materials have reached the stage where definitive studies can now be undertaken in man on virus causation and prevention of cancers (other than leukemias and lymphomas) i.e. the solid tumors. These advances are based on research progress in animal studies which have not only demonstrated that viruses cause a variety of tumors, but that in some instances prevention of the tumors can be achieved by vaccination. As with several animal tumors, it may be possible to isolate human cancer-causing viruses from man, and this search continues very actively. However, with other types of virus-caused tumors, it is known that virus cannot be found in the tumor, and indirect means must be used to demonstrate that a particular virus produced the tumor. New approaches and technologies are now sufficiently advanced to be ready for application to human studies.

Three new techniques identify the virus responsible for causing each of several animal tumors with DNA-viruses (e.g., 13 of the 31 adenoviruses, many of which also produce colds and gastrointestinal upsets in man). Four new techniques identify the virus responsible for causing other animal tumors with RNA-viruses (e.g., certain cancers of muscle, bone or other connective tissue). These indirect techniques permit identification of the virus that originally induced the tumor even though the virus itself is no longer present in the tumor.

To apply these techniques in the study of human cancers, it is necessary to develop capability of making field studies in populations of the natural histories of human cancers and associated viruses in their natural ecologies, plus expansion of related laboratory capabilities. With establishment of this population resource, studies can also be initiated on cancer causation by chemicals plus viruses, both the DNA and RNA types. The laboratory testing and field studies investigations are costly because of expense of virus identifying agents and complex logistics, but to a greater extent because they require highly skilled manpower for performing the testing and providing large amounts of carefully produced and well monitored sources of susceptible cells, tissues and sera.

National Cancer Institute

Research Development and Radiation Therapy
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| In-House..... | -- | -- | -- | $80 | $80 | $100 | $120 | $120 |
| Contracts..... | -- | -- | -- | $2,000 | $3,300 | $3,600 | $3,900 | $4,500 |
| Total..... | -- | -- | -- | 2,080 | 3,380 | 3,700 | 4,020 | 4,620 |
| Related grants..... | $5,640 | $5,922 | xx | xx | xx | xx | xx | xx |
| No. of positions... | 0 | 0 | 0 | 4 | 4 | 5 | 6 | 6 |

The development of megavoltage therapy units about fifteen years ago has led to improvement in this form of therapy. With the availability of super voltage radiation sources such as cobalt units, linear accelerators, and betatrons, marked improvement in the cure rate of certain malignancies to radiation therapy has been noted. At the same time electron beam therapy was found to produce cures in superficial tumors such as may be found in the head and neck. During this period of time, engineering and radiation physics advances indicate that an optimal dual purpose linear accelerator can be developed which will encompass all of the advances found over the last few years in a single machine. This will provide the best and most advanced source of ionizing radiations to treat human cancer by this modality. These instruments will be provided to outstanding Radiation Therapy Departments which have adequate radiation physics and radiation biology research and support capabilities, associated with approved graduate training programs.

New and increased knowledge has indicated that improved, highly sophisticated linear accelerators can be obtained which will provide better radiation therapy to the cancer patient with radio-curative tumors. These accelerators will be able to produce an electron beam or an X-ray beam. The development of new radiation therapy machines is expensive and the potential market so limited that government support is required. At the same time public and private institutions must be helped in obtaining new, sophisticated and very expensive radiation sources. During the past year specifications have been developed for an advanced linear accelerator designed for radiation therapy. The building of a prototype instrument with subsequent clinical testing has been postponed because of a lack of funds.

In addition, the use of particulate radiations, particularly fast neutrons and negative pi-mesons, has been a matter of continuing review and study. Recent results strongly indicate that a clinical trial utilizing fast neutrons should be performed. A joint program with the Atomic Energy Commission and the National Cancer Institute is under active consideration. Funds estimated through 1974 are needed in order to complete the development of the linear accelerator as well as to procure them for clinical radiation therapy research.

National Cancer Institute

Cancer Research Centers
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants.. | $11,886 | $12,590 | $13,310 | $17,242 | $21,239 | $26,306 | $29,447 | $32,668 |

Cancer research centers are institutions (or segments of institutions) concerned solely with cancer research. They are important to the research effort because they can bring many diverse skills as a team to perform research aimed at solving the cancer problem. Because their focus is cancer, they offer a better chance of finding the answers than can be achieved by project grants alone.

While the National Cancer Institute has been supporting 25 centers, most of these are quite small, not balanced, and often are concerned only with a single aspect of cancer research. The five or six fairly well developed centers are concentrated in the East, with one in Texas. The Institute wishes to strengthen the existing centers as well as to establish centers in the South, Middle West and Far West where there are too few or no centers at all.

The contributions of cancer centers to solving the cancer problem are of great importance and varied. Important advances have been made in the treatment of leukemia, in improved techniques for treating solid tumors with surgery, radiation and chemicals and in concepts in use of drugs under revised regimens which take advantage of new theories of how cells divide and reproduce. The more fully developed centers do this against a background of knowledge acquired in the laboratory which will provide the base for clinical treatment of the future.

Because of the limited number of specialized cancer treatment centers, many cancer patients being seen for the first time pass through general treatment clinics or through the offices of their private physicians. The professional persons observing the patient may have had little opportunity to become familiar with modern cancer diagnostic and treatment techniques. As noted above most of the centers are now located in the northeastern area of the United States. Thus residents of other geographical areas are deprived of the benefits of the advanced knowledge and techniques already available to individuals in locations where centers now exist. It is vitally important that our most advanced diagnostic and therapeutic techniques be extended rapidly to all cancer sufferers. The complexities of cancers require a coordinated effort on the part of scientists ranging from those undertaking basic research in cancer biology to research clinicians, and finally to clinicians responsible for the care and treatment of cancer patients. To do this, medical schools, specialized cancer facilities, practicing physicians and community medical services must participate in integrated programs of research and training. With this in mind it is planned to develop a number of cancer research centers which will combine the fundamental research competence of the university medical school with the long experience and skills of the best cancer institutes.

National Cancer Institute

The Lung Cancer Task Force
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| In-House..... | -- | -- | $300 | $596 | $818 | $967 | $1,068 | $1,111 |
| Contracts..... | -- | -- | 1,100 | 3,102 | 6,184 | 8,272 | 9,366 | 10,467 |
| Total | -- | -- | 1,400 | 3,698 | 7,002 | 9,239 | 10,434 | 11,578 |
| Related grants..... | $2,145 | $2,396 | xx | xx | xx | xx | xx | xx |
| No. of positions.... | 0 | 0 | 22 | 32 | 42 | 50 | 55 | 60 |

In his 1968 Health Message, the President called for the establishment of a Lung Cancer Task Force for the purpose of planning and implementing a broad research program on human lung cancer. Extensive plans for an integrated program approved by the Lung Cancer Task Force proposes major research efforts in four areas: (1) smoking and tobacco; (2) lung cancer causation other than smoking, including air pollution and host modification aspects; (3) diagnosis; and (4) treatment. Central to all areas in addition are extensive biometric and epidemiologic efforts. A subcommittee of the Task Force currently is studying techniques for developing a less hazardous cigarette. Since this program logically embraces issues broader than cancer causation, research on heart disease, chronic degenerative lung diseases, and other biological effects as well as cancer will be studied on a unified basis and supported jointly with other organizational components of NIH, the Division of Environmental Health Sciences and the National Heart Institute.

Means for evaluating modified cigarettes and/or tobacco must be established; biological and chemical assay systems must be selected and developed as well as a continuing system for monitoring populations and cigarettes actually smoked. The assay systems will also be used to evaluate inventors' claims for improving devices. To establish such systems requires development of standardized screening capability, computerized data handling of carcinogenesis technical data (unfortunately not yet in existence), and pharmacology and toxicology efforts, including collection of greatly improved dosage information. Because of the significance of co-carcinogenic and promoting effects of various chemical and viral agents, multi-disciplinary screening systems will also need to be developed plus extensive pathology capability. Similar efforts are required in the non-smoking area.

Considerable research in the diagnostic area is required, as leads are few. In therapy, several on-going activities of the Chemotherapy Program can be enlarged to encompass additional efforts in the treatment of lung cancer.

To implement this complex, integrated program will require many specialized skills: biologists, chemists, epidemiologists, computer programmers, virologists, physicians, etc. The task is difficult and lengthy and will require long-term commitments if investigators are to be interested in working in this program area.

National Heart Institute

Atherosclerosis and Coronary Artery Disease
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | $24,336 | $23,756 | $23,956 | $26,300 | $29,000 | $31,900 | $35,000 | $38,500 |
| Direct operations: | | | | | | | | |
| In-House..... | 0 | 0 | 0 | 100 | 200 | 400 | 500 | 500 |
| Contracts.... | 0 | 0 | 0 | 2,900 | 13,800 | 22,600 | 32,500 | 34,500 |
| Total..... | 24,336 | 23,756 | 23,956 | 29,300 | 43,000 | 54,900 | 68,000 | 73,500 |
| No. of positions.. | 0 | 0 | 0 | 5 | 10 | 15 | 20 | 20 |

The prevention of arteriosclerosis and its complications is the highest priority goal of the Heart Institute. There is a severely excessive mortality and morbidity from the disease in the U.S.A. that is not only unnaturally high, and abnormally premature but that should be amenable to reduction. Reduction below the age of 65 is clearly anticipated; appreciable reduction beyond the age of 75 is uncertain. A 25% reduction below the age of 65 is realistic and would save 40,000 productive lives per annum. The population distribution would not be grossly distorted as a result. An approximation to the population profile of Sweden could be anticipated and would be a desirable goal. Cost studies indicate that prevention is the most economical and logistically feasible approach to premature deaths from atherosclerosis. Other methods of salvage have real but more limited applicability.

Two major organized areas of research activity are either underway or proposed:

a. Diet Study. A definitive study is proposed of the effect of diet modification on the prevention of arteriosclerosis. Feasibility of diet change in a free-living population has been demonstrated in a study just now completed. A five-year test of the effect of diet modification on open population will only be done if it appears a clear answer will be obtained and if applicability of its findings can be expected. Designs are now under intensive examination by staff and panels of outside experts. It is suggested that cohorts greater than 30,000 men at annual operating costs of as much as $35,000,000 may be needed. The cost includes biometric, training, and other ancillary research needs. Design requirements could increase this amount several fold. A rough economic benefit analysis indicates that a 10% reduction of mortality below the age of 65 would correspond to an annual savings of up to $1 billion in cumulative earnings. In the event that an open population study is deemed inadvisable, closed population studies, one of which has begun, will have to be expanded. At present more than 10,000 subjects are expected to be required in such a test. The costs of a closed study will be less than an open one, but its applicability may be more limited.

b. Drug study. These are detailed in a separate summary.

The base of grant research in arteriosclerosis and its prevention, diagnosis and treatment is projected to grow moderately forming the substrate from which all other knowledge arises. About two thirds of such activity in the USPHS is within the Heart Institute. Major new emphases within the program area are possible.

It should be noted that the Artificial Heart-Myocardial Infarction Program, organized research directed primarily to the treatment of atherosclerotic heart disease, is considered separately from this report.

National Heart Institute

Heart Drug Studies
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | $3,433 | $3,820 | $3,820 | $5,506 | $5,456 | $7,275 | $10,080 | $7,976 |
| Direct operations: | | | | | | | | |
| In-House..... | 0 | 0 | 0 | 0 | 0 | 75 | 100 | 100 |
| Contracts..... | 780 | 780 | 780 | 807 | 900 | 900 | 850 | 400 |
| Total..... | 4,213 | 4,600 | 4,600 | 6,313 | 6,356 | 8,250 | 11,030 | 8,476 |
| No. of positions.. | 0 | 0 | 0 | 0 | 0 | 4 | 4 | 4 |

Drugs that lower blood fats and thus potentially decrease atherosclerosis are another possible means of preventing premature expression of the disease. There are two types of trials of such drugs: secondary, to prevent recurrence of a heart attack, and primary, to prevent or delay the occurrence of a first heart attack or other serious manifestation of atherosclerosis.

The current Cooperative Study of Drugs and Coronary Heart Disease is a large-scale, cooperative clinical study on the secondary prevention of myocardial infarction by four hypocholesteremic drugs. Its primary objective is whether these drugs that reduce the concentration of blood lipids, or fats, are capable of improving survival among patients with coronary heart disease. A second objective is to determine whether the degree to which these drugs lower serum lipids is correlated with their effect on mortality and heart-attack rates. By studying just as intensively the individuals in the study who do not receive lipid-lowering agents, the investigators will obtain valuable further information concerning the outlook for men who have survived an initial myocardial infarction.

In human terms, if the effectiveness of these drugs is in fact related to their ability to lower blood fats, it can be calculated that such drugs might be able to reduce the number of fatal recurrent heart attacks by 25 percent or more. This would have obvious and important consequences for the three million or more Americans with definite coronary heart disease and the additional two million suspected of having it. Furthermore, demonstration of the principle that drugs which lower blood lipids can improve survival would stimulate the development of still more satisfactory lipid-lowering drugs for the treatment and prevention of coronary heart disease.

Congress provided funds in 1966 and 1967 to fill out the total of 55 clinics anticipated in the study plans. During 1968 and 1969 that plan calls for these clinics to recruit approximately 8,400 patients to be followed for a 5-year period. Funds shown for 1970 would allow this study to proceed as planned.

The possibility that by 1972 there may be the need to mount a similar drug test for the primary prevention of heart attacks in high risk groups is anticipated. The projection is for a full operating cost of 7.5 million dollars annually. Primary prevention trials are more expensive than secondary trials since the number of subjects required is greater.

National Heart Institute

Artificial Heart - Myocardial Infarction Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Direct operations: | | | | | | | | |
| In-House..... | $210 | $350 | $500 | $600 | $700 | $800 | $900 | $1,000 |
| Contracts..... | 13,574 | 13,042 | 14,892 | 20,400 | 41,800 | 54,200 | 64,100 | 64,000 |
| Total.... | 13,784 | 13,392 | 15,392 | 21,000 | 42,500 | 55,000 | 65,000 | 65,000 |
| No. of positions.. | 46 | 37 | 37 | 37 | 50 | 50 | 50 | 50 |

The Artificial Heart - Myocardial Infarction Program operates research and development programs in three areas: Mechanical Circulatory Assistance (MCA); Cardiac Replacement (CR); and Myocardial Infarction (MI). The allocation of funds among these is based on an assessment of need and probability of practical application.

Mechanical Circulatory Assistance (MCA)

It is the goal of this program to provide a family of devices that will meet clinical needs for mechanical circulatory assistance, both short-term and long-term, including a permanent implantable assistance device. Five types of devices have had minimum clinical trials. The principal impediment to development of pumps or oxygenating devices is lack of ideal structural material. Recent developments in polyelectrolyte, hydrogel, and anticoagulant chemistry offer promise of overcoming this barrier. Permanent assistance devices require development of energy sources and engines. Thermal engine or piezo-electric systems appear promising. Limitations on resources are restricting our ability to carry different materials, pump and system design into systematic development and testing. The expansion requested will enable the Program to: (1) accelerate material research and development to the level of specific components, (2) accelerate research in coupling engine and pumping subsystems, (3) begin production engineering of total systems, (4) begin systematic biologic testing and evaluation of total systems, (5) train medical and paramedical personnel in the use of mechanical circulatory assistance.

Cardiac Replacement (CR)

Many of the scientific problems in development of the totally implantable artificial heart (AH) are similar to those in other devices; for example, materials, pump design, control mechanisms, and the like. However, there are special problems of design which accompany the concept of total replacement. In addition, if cardiac replacement therapy is to be accomplished by cardiac homotransplantation (CT), it will be necessary to: (1) expend more effort in the field of cardiac preservation; (2) support systems of isolated hearts for preservation outside the body; (3) develop techniques for long-term circulatory assistance on which there would be a particular need for better systems of oxygenation; and (4) upgrade registrations and communications of activity. These areas have not received special consideration previously.

THE MYOCARDIAL INFARCTION PROGRAM (MI)

It is the aim of this program to reduce mortality and morbidity in patients with acute myocardial infarction. In the first two years of its operation the beginning of a network of Myocardial Infarction Research Units has been implemented. By the beginning of FY'69 we hope to have eight or nine such units in operation. With the current budgetary restraints we have been able to implement only one other project. This project was concerned with the development of suitable experimental animals models of acute myocardial infarction. Further expansion in this program is based on the need: (1) to develop the full national network of Myocardial Infarction Research Units, and (2) to implement projects in sudden death, cardiogenic shock, pathology of myocardial infarction, and in evaluation of pharmacologic and mechanical therapeutic methods.

These programs are relatively new and are in a growth phase. They have not reached stable levels of operation. Increments based only on cost of living would not permit us to implement interdependent facets of the Program.

National Heart Institute

Cardiovascular Research and Training Centers
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | $800 | $800 | $1,050 | $10,800 | $14,800 | $18,000 | $30,000 | $38,000 |
| No. of positions.. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

During fiscal years 1966, 1967, and 1968, the NHI budget included $800,000 each year for specialized Cardiovascular Research and Training Centers. These funds have been used to award grants for planning at twelve institutions.

In order to provide an adequate base for the establishment of approximately twelve centers during the next 5-6 years, it is proposed that an additional 12-15 grants for planning be awarded during the next three-year period, i.e., during fiscal years 1969, 1970, and 1971.

The centers currently being planned are to be centers of excellence with a corps of scientists capable of imaginative and creative investigation of the diverse problems of human cardiovascular diseases. Organized under outstanding leadership, scientists from basic and clinical disciplines will work in sufficiently close proximity and with a degree of integration of their activities such that ideas and technical advances may be continuously exchanged and evaluated in a critical environment. The stimulation to the individual scientist made possible by the physical and intellectual proximity of others dedicated to the same ultimate goal, but possessed of the special knowledge and skills of other disciplines, will foster the coordinated investigations required for the solution of difficult and challenging problems. These centers will include, or be closely allied with, personnel and facilities essential for the conduct of sophisticated diagnostic and therapeutic procedures; thus they will provide a rich environment for training both clinical and laboratory personnel. The development of such centers will accelerate and increase our capacity to meet critical manpower shortages.

Using funds currently available, the Institute expects to provide the first center with some operational support during FY 1968, or, at the latest, during FY 1969. However, four other centers should be provided with at least limited operational support by FY 1970. Otherwise, the major thrust of planning activities initiated during FY 1966 and 1967 is likely to be greatly diminished.

Additional centers currently being planned will require operational support during FY 1971 and 1972, and the planning activities to be initiated during FY 1969, 1970 and 1971 will result in the need for additional operational support beginning in FY 1973.

Initial operational support is projected at $2.0 million per center, and this requirement is likely to increase to approximately $4 million during the first 3-5 years of operation.

Finally, a major bottleneck in the development of this program is a critical shortage of space to adequately house these centers. Funds for construction, estimated at approximately $4 million per center, should be included in the program plan for the Division of Research Facilities and Resources.

National Heart Institute

The National Blood Resource Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Direct operations: | | | | | | | | |
| In-House..... | $33 | $75 | $125 | $200 | $225 | $250 | $275 | $275 |
| Contracts.... | 1,726 | 2,717 | 2,667 | 3,600 | 5,650 | 6,250 | 6,925 | 7,725 |
| Total..... | 1,759 | 2,792 | 2,792 | 3,800 | 5,875 | 6,500 | 7,200 | 8,000 |
| No. of positions.. | 5 | 5 | 5 | 8 | 10 | 10 | 10 | 10 |

Human donor blood and blood fractions are important in the modern treatment of disease. To provide for all the blood and blood component needs of a growing American population, three general aspects of blood handling require improvements in technology: 1) preservation; 2) fractionation; and 3) distribution. No insurmountable scientific problems obstruct the way to meeting these needs from the present supply.

Recent scientific advances include the following: 1) Chemical additives that double the shelf life of blood; 2) freezing techniques for long-term preservation of blood that may also be applicable to the preservation of blood platelets; 3) methods for producing a highly potent and effective antihemophilic factor that may be adaptable to large-scale production; and 4) advances in computer and automation technology that offer an opportunity for greatly improving efficiency and productivity of the blood-handling system, reducing waste and saving many millions of dollars.

During the years 1968-69 the following objectives will be pursued: 1) continued investigation of new blood preservatives; 2) feasibility study of computer-based inventory control and blood information system; 3) large scale production of anti-hemophilic factor; and 4) improvement of platelet and red cell preservation.

During the years 1970-74, anticipated projects include 1) the institution of a prototype computer-based regional or national blood inventory and information system if its feasibility is demonstrated; 2) automation of steps involved in blood fractionation and freezing procedures; 3) the development of facilities for storage of frozen blood and blood products at very low temperatures; and 4) research to establish new medical uses for blood components.

Urokinase: Since thrombosis may be a major causative factor in as many as one million deaths a year in America, the public health and economic implications of a successful treatment are enormous. Urokinase, a clot-dissolving agent derived from human urine, shows great promise. Controlled clinical trials are being undertaken to study its usefulness against pulmonary embolism over the next 2-3 years. Should results be successful, trials in myocardial infarction and other thrombotic diseases will be undertaken.

Budget reductions would delay the development of systems to provide for existing blood requirements, future predictable needs and would delay for some years investigations leading to an adequate treatment for thrombosis.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Dental Research Institutes (Centers)
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants... | $3,000 | 3,000 | 3,000 | 5,500 | 6,500 | 8,000 | 10,500 | 12,500 |

The staggering costs of oral health problems and the inability of the Nation's resources to keep pace with growing needs for their resolution dictated a critical appraisal of related research, educational, and service activities. Undertaken some three years ago, this study identified as a fundamental problem an inadequate scientific base for dental investigations. Arising from the absence of a critical mass of investigators and compounded by a dearth of full-time dental faculty, it threatened to cast many dental schools in the mold of technological institutions. The concept of establishing university-based, dental research institutes evolved as a consequence of this appraisal. Such centers will provide environments not only for broad, interdisciplinary, creative research but also for the extension of opportunities for research training and dental education.

Drawing on the total resources of their parent universities, and funded by grants from a special appropriation approved by the Congress, five such centers are now in varying stages of development. These research institutes are located at the Universities of Alabama, Michigan, North Carolina, Pennsylvania, and Washington. Applications are now under review for the development of new experimental models in the form of multi-university complexes.

Characterized by innovation, the program to establish dental research institutes is designed to build on existing strengths, provide for participation of a broad range of sciences in the study of oral health problems, and interact with the research and educational programs of the parent university. In addition to contributing to new knowledge, such centers are expected to increase research and academic manpower in areas related to dentistry. Thus, by strengthening the scientific content of the undergraduate curriculum, dental education will also be improved. Moreover, through their strategic geographic deployment, these centers will speed the application of research findings to clinical use through continuing education of the dental profession.

Substantially increased support for this program is urgently needed at this time to assure the orderly growth of this vital national resource.

NATIONAL INSTITUTE OF DENTAL RESEARCH

SPECIAL ORGANIZED PROGRAMS IN DENTAL CARIES

Affecting nearly all Americans at some time during their lives, dental caries is the chief cause of tooth loss under age 35. If all cavities incurred each year could be filled, remedial care would cost about $10 billion. Even if this economic factor posed no obstacle, the distressing fact is that, if all those in need of dental care were to seek it, they would literally overwhelm the limited available professional manpower. Yet, as a consequence of the rising health expectations of the American people, demand for oral care is certain to increase. The magnitude of the problem thus imposes a stern need to develop new and more effective preventive procedures as well as to improve restorative materials.

Directed at achieving improved care and ultimate prevention of this universal disease, a three-pronged research program encompasses (1) the evaluation and early application of selected techniques of topical fluoride therapy, (2) an intensified interdisciplinary approach to the caries problem through a newly-established Caries Task Force, and (3) the development of new restorative materials.

Since only 40 percent of the Nation's population has the benefit of fluoridated drinking water, other techniques must be sought to extend the protective effects of fluoride. One such means is the application of fluorides topically to the teeth. A method currently under study employs a fitted mouthpiece by which fluoride is applied directly to the teeth as a gel. Following successful animal experiments, field trials of this technique in an area with a fluoride-deficient water supply demonstrated an 80 percent reduction of new tooth decay among school children. The mouthpiece was worn for six minutes each school day over a two-year period. A current study is examining whether there are additive effects when this treatment is employed in a community already protected by fluoridated water. The third study in this series seeks to learn whether use of the gel by preschool children, many with little or no tooth decay, provides a foundation for defense that will be maintained in later life. These evaluations are expected to be completed within the next three years, by which time guides will be available for the most effective application of this preventive measure.

The development of other types of preventive measures will be explored by a newly-established Caries Task Force. This organized effort will encompass clinical and epidemiologic trials as well as basic research. The microbiological approach, which is a principal focus of the task force, is discussed in the attached statement on the prevention of caries through control of plaque formation.

Pending the complete eradication of caries, the development of improved restorative materials is a practical necessity. Because they do not bond properly, present materials often have to be replaced. Such failures add both to the dental manpower deficit and the cost of care. Expanded efforts in this program area are described in the attached statement on new restorative materials.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prevention of Caries Through Control of Plaque Formation
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants..... | $ 25 | 100 | 100 | 200 | 250 | 350 | 400 | 500 |
| Direct operations: | | | | | | | | |
| In-House..... | 110 | 120 | 150 | 500 | 560 | 620 | 700 | 800 |
| Contracts..... | --- | 50 | 50 | 250 | 500 | 800 | 1,000 | 1,200 |
| Total | 135 | 270 | 300 | 950 | 1,310 | 1,770 | 2,100 | 2,500 |
| No. of positions.... | 6 | 6 | 7 | 27 | 30 | 33 | 37 | 42 |

Dental caries involves an interplay of microbial, dietary, genetic, and other factors and thus poses a number of complex problems for research. Encouraging recent advances, particularly in the microbiological approach, point to further significant reductions in tooth decay in addition to those accomplished through fluoridation.

Supported principally by Dental Institute funds and largely reflecting the activities of NIDR scientists, these investigations have focused on the role of oral microorganisms and plaque in the etiology of caries. They have recently culminated in the demonstration of the essential role of specific strains of streptococci in initiating the caries lesion.

In brief, these organisms are characterized by (1) their ability to adhere tenaciously to the enamel surface; (2) their preference for a sucrose type of sugar for growth; and (3) their capacity for producing large amounts of acid. The ability of these bacteria to adhere to the tooth surface is enhanced by their production of dextran, a type of polysaccharide. This substance is secreted as a gummy coating which forms the matrix of the bacterial plaque deposits.

NIDR scientists, in collaboration with investigators at Merck Sharp and Dohme Research Laboratories, recently isolated an enzyme (dextranase) which appears to dissolve dextran produced by the cariogenic streptococci. Caries has been almost completely prevented in hamsters by incorporating small amounts of this enzyme in their food and water. If these preliminary results in animal trials are borne out in humans, this work represents one of the most significant new approaches to preventive dentistry in recent years. Clinical trials will be initiated shortly and expanded as additional funds become available. Analogous approaches to the possible role of other bacterial polysaccharides in plaque as etiologic factors in oral diseases are being pursued.

Substantially increased support for this program at this time may very well lead to the development of preventive therapies which will be both safe and easily within the economic reach of everyone.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Development of New Restorative Materials
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $511 | 520 | 520 | 600 | 680 | 780 | 900 | 1,050 |
| Direct operations: | | | | | | | | |
| Contracts..... | 302 | 400 | 400 | 900 | 1,400 | 1,600 | 1,800 | 2,000 |
| Total | 813 | 920 | 920 | 1,500 | 2,080 | 2,380 | 2,700 | 3,050 |

The treatment of decayed teeth continues to represent the major expenditure for dental care in the United States. Much of this cost relates to the inadequacy of currently available filling materials which frequently crack, loosen, or otherwise fail, thereby often requiring repeated repair or replacement. Not only does this impose a prohibitive economic burden, but it also represents a grossly inefficient utilization of already scarce dental manpower. Until better preventive measures and agents are identified, the answer to this problem lies in a major research effort to develop markedly improved restorative materials.

Accordingly, high priority is being given to the development of an effective adhesive filling. Once such a material is available, it will have far-reaching uses, permitting more effective, longer-lasting treatment at less cost. Not only invaluable for restorative fillings, an adhesive material also would be useful in otherwise time consuming orthodontic procedures. Moreover, applied as a protective film over vulnerable tooth surfaces, it might serve to inhibit or prevent caries and calculus formation.

All dental biomaterials must meet exacting requirements to function in the complex environment of the mouth. Major effort is, therefore, being centered on examining the physical and chemical properties of synthetic and biological materials and their relations to the oral environment. Related collaborative research is currently seeking to encourage the development of standards for adhesion to tooth surfaces, particularly in an aqueous environment. These explorations are being undertaken in concert with other institutions and agencies, including the National Bureau of Standards and the Veterans Administration.

Among the various approaches employed in this research effort is the study of adhesive properties of barnacle cement, including its structural and chemical characterization, and its synthetic preparation. Unlocking the secrets of barnacle cement could have an economic impact far beyond its sizable dental application.

Biomaterials research is now at a point of critical momentum. The interest of engineers, metallurgists, polymer chemists, and other specialists from industrial and university laboratories has been increasingly attracted to this important area of endeavor. Many productive avenues exist for channeling this interest.

National Institute of Arthritis and Metabolic Diseases

Endocrine and Diabetes Hormone Developmental Research Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| Contracts..... | $288 | $390 | $390 | $2,025 | $3,150 | $3,350 | $3,750 | $4,000 |
| Related grants..... | $2,179 | $2,200 | xx | xx | xx | xx | xx | xx |
| No. of positions... | 0 | 0 | 0 | 3 | 4 | 4 | 4 | 4 |

The Scientific Problem:

Although the number of patients with specific endocrine deficiency diseases is small, 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. Since osteoporosis (thinning and weakening of the bones with age) affects 14 million people, diabetes affects 6 million and intestinal diseases require the second largest number of physician home visits, it is estimated the number of more than 40 million people reflects the morbidity and lost income related to these diseases with some degree of hormone function disturbance.

Opportunities for Advance:

Opportunities for more rapid progress in peptide hormone research have been provided by two recent, relative breakthroughs: 1) development of the method of radioimmunoassay, and 2) improvement in physical-chemical methodology permitting preparation by extraction of many hormones now active in man, in pure, or isotopically labeled or active fraction form.

Numerous examples may be cited of areas of peptide hormone research which will be stimulated and strengthened by direct, concerted efforts at support: 1) human pituitary hormones, extending investigation of their effects in growth disorders of many types, in fertility and sterility problems, and (through the National Pituitary Agency supported by this Institute) exploring new methods of preparation of badly needed growth hormone, 2) gastrointestinal hormones, particularly studying the bearing secretin, gastrin and pancreozymin have on ulcerogenesis, liver function, gallbladder disease and diabetes, and 3) diabetes-related hormones, for development of better knowledge of insulin antagonism, development of better diagnosis through new assays and tests, and synthesis of additional effective oral drugs.

Program Plan:

In this area of special opportunity, the NIAMD will select and develop certain investigator-initiated projects and provide contract support to solve the more urgent, practical diagnostic and treatment oriented problems. Where needed for assessment of the value and usefulness of the methods and treatments devised, collaborative clinical studies will be initiated.

National Institute of Arthritis and Metabolic Diseases

Artificial Kidney Program
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| Contracts..... | $3,900 | $6,600 | $6,600 | $7,900 | $8,400 | $8,900 | $9,200 | $9,400 |
| Related grants..... | $6,031 | $6,100 | xx | xx | xx | xx | xx | xx |
| No. of positions... | 12 | 15 | 15 | 17 | 19 | 19 | 19 | 19 |

In the United States, each year an estimated 50,000 individuals die due to progressive irreversible kidney failure. A majority of these end-stage kidney disease patients were originally afflicted with three major categories of primary kidney disease, glomerulonephritis, pyelonephritis, and hypertensive kidney disease. The only available treatments for the common terminal pathway of these disorders, end-stage kidney disease, are renal transplantation and chronic hemodialysis. Each year 8,000 new end-stage patients are considered suitable candidates for maintenance through chronic hemodialysis.

NIAMD has a special integrated research and development program aimed at the development of improved and more effective dialysis hardware and methodologies and of methods for optimal rehabilitation of chronic dialysis patients. This Artificial Kidney Program is centrally directed, and its research and development contract projects have been stimulated directly by staff initiative. Among recent accomplishments are development of 1) a compact, highly efficient dialyzer with greatly decreased blood priming requirement and significantly lower dialysis time and cost, 2) multiple re-use techniques of artificial kidneys (without dismantling and resterilization) which greatly reduce the cost and work involved in home dialysis, and 3) a unique, disposable, hollow fiber capillary kidney which recently reached clinical trial stage.

In addition to ongoing development of better hardware and methodologies, the Program is pursuing the following opportunities for further research gains; 1) Determination of the effectiveness of various special, low-protein diets in patients in advanced stages of renal insufficiency and assessment of their merit in association with infrequently applied hemo- and peritoneal dialysis; 2) identification of chemical metabolites apparently responsible for toxic symptoms in chronic renal disease; 3) definition of the pathogenetic mechanisms of the serious accompanying features of renal failure during chronic dialysis, peripheral neuropathy, calcium dystrophy, and anemia.

Hardware and methodology development have been pursued at a budgetary level consistent with 1) the limitations of current technologic state of the art, and 2) the current state of knowledge concerning chronic uremia. In view of the resulting advances new opportunities and needs present themselves now for specific organized clinical studies related to comparative clinical evaluation of dialysis methods and the long-term complications of dialysis.

Current DHEW plans and introduced legislation concerning expanded use of chronic hemodialysis make it imperative that studies be initiated to define as carefully as possible the effects of dialysis in chronic uremia with particular attention to the serious accompanying clinical features described above. A limited number of special clinical research projects under a coordinated protocol will be initiated under contract support for detailed, intensive biochemical and physiological studies for 1) investigation of the pathogenesis of peripheral neuropathy, calcium dystrophy and anemia, 2) determination of base-line criteria for truly irreversible renal failure necessitating institution of chronic dialysis, and 3) comparative clinical evaluation of different diaylsis methodologies and apparatus.

National Institute of Neurological Diseases and Blindness
PERINATAL PROGRAM
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants | 3,203 | --- | --- | 200 | 400 | 400 | 500 | 600 |
| Direct operations: | | | | | | | | |
| In-House | 2,570 | 2,953 | 3,440 | 3,900 | 4,400 | 5,000 | 5,700 | 6,400 |
| Contracts | 900 | 6,000 | 6,000 | 6,200 | 6,400 | 6,500 | 6,600 | 6,700 |
| Total | 6,673 | 8,953 | 9,440 | 10,300 | 11,200 | 11,900 | 12,800 | 13,700 |
| Related grants | 3,300 | 3,400 | --- | --- | --- | --- | --- | --- |
| No. of positions | 229 | 245 | 248 | 282 | 243 | 301 | 308 | 315 |

This program comprises epidemiologic and laboratory investigations of factors operating during pregnancy and in early life to cause damage of the infant brain.

Each year an estimated 250,000 children are born with prenatally or perinatally determined impairment of brain function. Their lifetime deficiencies represent one of the Nation's largest health burdens. Because the effects on the unborn child of factors operating during pregnancy are easily overlooked, it has been difficult to obtain precise knowledge of what they are and how they produce injury.

The Institute is using two major approaches. A large cooperative effort, involving 14 medical centers and the Perinatal Research Branch of the NINDB, is obtaining information from a population of pregnant women and their babies. Data have been collected on about 60,000 pregnancies and the resultant babies over the past nine years. The first pregnant woman was admitted to the study in January 1959, and the last, in December 1965. The last baby was born in September 1966. Supervision and periodic observation of the children will continue at least until 1974. Although much of the data on the obstetric phase and from the early examinations of children are now being studied, it is not until the latter date that full use may be made of all the study data. In the meantime, however, an intensive analysis of all information now available is underway to characterize the study population, and to examine the quality and validity of the data. Coincident with these analyses, special studies have continued and are producing highly significant findings. From these preliminary findings, a number of special studies, and field trials of remedial and preventive measures can be developed.

To parallel these human observations, the Institute has developed a program of animal experimentation. Within the Institute's Laboratory of Perinatal Physiology in Puerto Rico, a primate colony has been established. Experimental manipulations of these pregnant monkeys are used to determine the mechanism of action of harmful factors and the means for the prevention of brain damage in the infant.

National Institute of Neurological Diseases and Blindness
STROKE
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants | --- | --- | --- | 200 | 400 | 400 | 500 | 500 |
| Direct operations: | | | | | | | | |
| In-House | --- | --- | --- | 200 | 500 | 1,000 | 1,400 | 1,400 |
| Contracts | --- | --- | --- | 300 | 1,000 | 2,000 | 2,000 | 2,400 |
| Total | --- | --- | --- | 700 | 1,900 | 3,400 | 3,900 | 4,300 |
| Related grants | 4,327 | 4,793 | --- | -- | --- | -- | -- | -- |
| No. of positions | -- | -- | --- | 3 | 5 | 7 | 8 | 8 |

This is a program to develop diagnostic techniques for detecting incipient strokes.

Many strokes might be prevented if one could detect antecedent arterial disease and impairment of cerebral blood flow. What is needed is a test which is inexpensive, easily done, without risk to the patient, and which could be included in the annual physical examination. There are two essential components of such a detection system: one is a means of detecting the actual physical condition of the artery; the other is a system for determining the adequacy of flow to various brain regions. At the present time, X-ray angiography and isotope detection techniques show great promise.

Angiography is performed by injecting an X-ray opaque (shadow producing) dye directly into the arteries of the brain. An X-ray taken as the dye courses through the vessel provides a clear shadow of the artery. Unfortunately the arterial injection is hazardous. Intravenous injection is not. However, special means for intensifying the shadow will need to be developed.

The isotope detection technique is used to determine regional blood flow. Inert radioactive gases are given to the patient to breathe. When the brain is saturated, the rate of disappearance of the gas from the brain is measured. These current techniques are complicated and slow. It is possible to develop a "gamma camera" which gives pictures of the entire head. As the radioisotopes appear in the brain, they are detected in a single picture. The development of these two methods, or other related techniques would be a major advance in detection of the stroke-prone individual. Evaluation can be done in a few minutes.

National Institute of Neurological Diseases and Blindness
INJURIES OF THE CENTRAL NERVOUS SYSTEM
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants | 350 | 425 | 1,040 | 1,500 | 1,750 | 2,000 | 2,250 | 2,500 |
| Direct operations: | | | | | | | | |
| In-House | | | | | | | | |
| Contracts | 850 | 770 | 1,483 | 2,050 | 1,700 | 1,800 | 1,900 | 2,000 |
| Total | 1,200 | 1,195 | 2,523 | 3,550 | 3,450 | 3,800 | 4,150 | 4,500 |
| Related grants | 1,576 | 1,130 | -- | -- | -- | -- | -- | -- |
| No. of positions | 5 | 7 | 10 | 12 | 12 | 14 | 14 | 14 |

This is a study of central nervous system injuries, how they can be prevented, and how their treatment can be improved.

Head injury represents a major cause of death and disability in both military and civilian population. The NINDB program is directed toward three major objectives: the prevention of head injury; the curtailment of progressive brain damage after the moment of impact; and the amelioration of sequelae.

Injury to the spinal cord is also a major physical and economic disaster. It is estimated that there are some 60,000-100,000 people with either paraplegia or tetraplegia resulting from injury and many more who have the same condition resulting from medical disease. Each of these injuries costs the patient about $50,000 and untold anguish to himself and his family.

Recent significant advances in understanding the causes of head injury have greatly reduced the frequency of these injuries in industry. Current research is leading to more knowledge about the nature and control of brain edema which occurs after injury and is one of the major problems in the care of patients today.

The NINDB program has four major elements. First, epidemiological surveys provide precise information regarding the circumstances surrounding injury, the therapy administered, and the outcome. These surveys will provide data essential for accident prevention and improvement in the management of the injured. Second, the study of the forces of head injury. What happens within the brain which results in physiological changes and loss of neural function? The answer to this question is essential for better understanding and improvement in the management of head injury as well as for better protective devices. Third, the development of clinical research centers for testing fundamental knowledge and adapting it to the active treatment of patient. The major objective, of course, is the prevention of progressive damage after injury and the resultant improvement of the long-range outcome. Fourth, the longitudinal study of head injury patients. It is important to define the post-traumatic syndrome--what causes it, and how it can be prevented. Such knowledge influences the management of head injury, determines factors which influence social and economic adjustment, and leads to remedial measures and rehabilitation.

National Institute of Neurological Diseases and Blindness
STIMULATION OF THE CENTRAL NERVOUS SYSTEM
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants | | | | 200 | 400 | 600 | 800 | 1,000 |
| Direct operations: | | | | | | | | |
| In-House | -- | 259 | 271 | 285 | 300 | 300 | 200 | 400 |
| Contracts | 98 | | | 200 | 400 | 600 | 800 | 1,000 |
| Total | 98 | 259 | 271 | 685 | 1,100 | 1,500 | 1,800 | 2,400 |
| Related grants | -- | -- | -- | -- | -- | -- | -- | -- |
| No. of positions | -- | 6 | 8 | 10 | 12 | 12 | 12 | 12 |

The purpose of this program is to design and build devices which will permit various types of external input to be connected to the central nervous system in a form which can be handled by the brain.

Man's only meaningful contacts with the external world are through his sense organs--the eye, the ear, the organs of taste and smell, and sensitive structures within the skin and viscera. Injury or a defect of one or several of these elements isolates the human nervous system from its environment, and incapacity results. Similarly, man's physical effectiveness depends largely upon the activation of his muscular system by the nervous system. When the central mechanisms for voluntary movement have become deranged, as in parkinsonism, cerebral palsy, or hemiplegia after stroke, varying degrees of helplessness ensue.

If the proper kind of device can be made to stimulate appropriate pathways within the nervous system, it might be possible to bypass the sensory end organ, or to accomplish a direct output to some effector other than the muscular system. Such a device might conceivably provide hearing for the deaf, or visual information for the blind.

Recent fundamental research has provided extensive information regarding the nature of the coded signals whereby information is transmitted to and within the nervous system. Temporarily implanted electrodes have been extensively used in animals and for human study, and many have been implanted for periods of years. A crucial need, however, is for a precisely located array of inert stimulating devices which will provide for long-continued direct contact between an external device and the nervous system.

This program is to develop a family of different kinds of devices which will be designed to fit specific body locations and fulfill specific functions. Prototypes of these devices can be expected to be developed within four to five years at 4.0 million dollars, but the ultimate devices will cost much more and take more time.

National Institute of Neurological Diseases and Blindness

ANTI-CONVULSANT DRUGS
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants | 106 | 111 | 117 | 623 | 1,129 | 1,600 | 2,100 | 2,600 |
| Direct operations: | | | | | | | | |
| In-House | 81 | 82 | 85 | 595 | 1,110 | 1,625 | 1,700 | 1,600 |
| Contracts | | 60 | 90 | 500 | 1,000 | 2,000 | 2,400 | 3,000 |
| Total | 187 | 253 | 292 | 1,718 | 3,239 | 5,225 | 6,200 | 7,200 |
| Related grants | -- | -- | -- | -- | -- | -- | -- | -- |
| No. of positions | 5 | 9 | 12 | 15 | 16 | 16 | 16 | 16 |

This program has been established to develop new and more effective anti-convulsant drugs for the treatment of epilepsy.

Within the foreseeable future, anti-convulsant drugs will be our most effective means for controlling epilepsy and certain related conditions characterized by overactivity of the nervous system. The development of an effective armamentarium of anti-convulsant drugs has been one of the most dramatic advances of this century in the treatment of a neurological disorder. Approximately 75 percent of these patients may be seizure-free with the judicious use of medications currently available. However, for many individuals, the use of these drugs is accompanied by uncomfortable or dangerous side effects, and for those patients for whom available drugs are ineffective, other measures must be found.

The period from 1930 to 1950 was a time of active drug development; many pharmaceutical companies developed, tested, and introduced new drugs. A recent survey, however, has indicated that because currently available drugs are reasonably effective and of low toxicity in most instances, and because of the costs of developing competing products, drugs which appear promising in laboratory testing are not now being subjected to clinical trial. Of 25 companies surveyed, only two expressed a strong positive interest, and eight indicated a willingness to participate in developing a program of clinical trials for promising drugs.

Over the past three years, the Institute has been developing a small collaborative program in epilepsy. This program includes a study to determine methods of case classification and drug evaluation preliminary to developing a full-scale program in drug testing. The program is now ready to be further developed and to begin testing new drugs. For example, there are certain newly developed anti-convulsant drugs which are different in structure and basic pharmacology from the diphenylhydantoin and phenobarbital groups now in common use. Their basic pharmacology in relation to seizures should be explored. As new analogues become available, they also should be subjected to prompt clinical trial. This can be accomplished through extension of the already well-developed pilot program in this area.

National Institute of Neurological Diseases and Blindness
INFLAMMATIONS OF THE BRAIN
(In Thousands of Dollars)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants | 526 | 529 | 555 | 1,100 | 2,400 | 5,700 | 6,000 | 7,000 |
| Direct Operations: | | | | | | | | |
| In-House | 1,147 | 1,147 | 1,547 | 1,347 | 1,547 | 1,747 | 1,900 | 2,100 |
| Contracts | -- | -- | -- | -- | -- | -- | -- | -- |
| Total | 1,673 | 1,676 | 2,102 | 2,447 | 3,947 | 7,447 | 7,900 | 9,100 |
| Related Grants | -- | -- | -- | -- | -- | -- | -- | -- |
| No. of Positions | 23 | 23 | 25 | 25 | 29 | 29 | 29 | 29 |

This program is a search for viruses which may cause degenerative disorders of the nervous system.

No cause or cure is known for an important group of neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, parkinsonism, and the subacute encephalitides of childhood. Recent scientific advances, however, suggest that a virus may be the cause of some of these disorders.

For multiple sclerosis, the time course of the disorder and its geographical distribution suggest a causative agent acquired in childhood but which lies latent for many years before manifesting itself in young adults. In this disease patterns of gamma globulin production by the brain are also suggestive of an unusual infectious process.

The recent success in transmitting kuru in a number of passages to chimpanzees and the still more recent passage of another form of chronic neurological disease, Jakob Creutzfeldt disease (subacute spongioform encephalopathy), to chimpanzees indicates that technology has advanced to the point where an all-out effort to detect the causative agent for other neurological diseases is justified.

To date, the major effort in this field has been made by a limited group of scientists, largely centered in the NINDB intramural program. The nature of this problem is so important that at least three separate laboratories should be working on the problem to make sure that research results are confirmed and that all avenues of approach are covered.

The problem of dealing with a highly infective agent which cannot be therapeutically controlled at the present time requires special facilities to safeguard both the scientist and the public. For this reason, extensive construction will be necessary in building holding facilities for the experimental animals, particularly large primates. Laboratories will be required in these facilities which are isolated from the animals and from other facilities so that the risk of spreading infection is held to the absolute minimum. Strict safety control is a major requirement for this research effort. The availability of such facilities will be one of the controlling factors in the prosecution of this endeavor.

National Institute of Allergy and Infectious Diseases

TRANSPLANTATION & IMMUNOLOGY
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Grants | 3,041 | 3,240 | 3,800 | 4,400 | 5,000 | 5,800 | 6,500 | 6,900 |
| Direct Operations | | | | | | | | |
| In House | 600 | 736 | 1,000 | 1,000 | 1,100 | 1,100 | 1,200 | 1,200 |
| Contract | 1,452 | 2,300 | 3,300 | 3,800 | 4,200 | 4,600 | 5,000 | 5,000 |
| TOTAL | 5,093 | 6,276 | 8,100 | 9,200 | 10,300 | 11,500 | 12,700 | 13,100 |
| No. of Positions | 16 | 16 | 26 | 27 | 28 | 28 | 29 | 29 |

The transplantation of human organs has excited great popular and professional interest. The brilliant surgical achievements of kidney, heart, and liver transplants have overshadowed the universal and far more difficult and crucial problems of organ rejection. Recognition of the foreign nature of an invader (whether it is a life-giving organ transplant, or life-destroying bacteria) is controlled by immunological reactions--the rejection phenomena.

Rejection of an organ can be minimized by tissue matching, not unlike the familiar blood-typing, but more complicated and less well-understood. The residual unescapable reaction can be further reduced by immunosuppressive measures involving drugs and complex biological substances (e.g., anti-lymphocyte sera and transplantation antigens). Critical also to the practical operation of a system for supplying organs is the problem of preserving the organ from a cadaver until it can be transplanted into a physiologically suitable, properly matched recipient. Trained personnel for tissue typing, laboratory surveillance of patients, development and evaluation of new methods are in short supply.

Leucocyte typing techniques and reagents have been developed as practical but incomplete answers to the tissue matching problem. Development and evaluation of immunosuppressive drugs and drug regimens is an essentially open-ended problem on which fair progress has been made. Biological immunosuppressive measures, rather than drugs, have greater promise of efficacy with much reduced dangerous side reactions; but the state of knowledge is still relatively primitive. Organ preservation is a multi-faceted open-ended research problem on which definite practical progress has been made. Training of personnel for research and evaluation studies will be encouraged, both by preceptorship arrangements on contracts and by the more formal mechanisms of selected training grants and fellowship awards.

National Institute of Allergy and Infectious Diseases

VACCINE DEVELOPMENT
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Grants | 2,268 | 2,500 | 2,600 | 2,800 | 3,000 | 3,300 | 3,500 | 3,780 |
| Direct Operations | | | | | | | | |
| In House | 1,150 | 1,354 | 1,500 | 1,550 | 1,600 | 1,700 | 1,750 | 1,820 |
| Contract | 6,700 | 5,200 | 6,900 | 7,450 | 7,900 | 8,500 | 8,950 | 9,500 |
| TOTAL | 10,118 | 9,054 | 11,000 | 11,800 | 12,500 | 13,500 | 14,200 | 15,100 |
| No. of Positions | 65 | 65 | 67 | 67 | 67 | 68 | 68 | 68 |

Viral diseases, as a group, still remain almost completely untouched by the modern miracle drugs. Respiratory viral infections are a significant cause of death in infants and children, and of enormous disability and lost time in all age groups. At present, the only clear, practical solution to this mass problem is by immunological methods--the development and evaluation of vaccines.

The oral, live adenovirus type 4 vaccine developed by the program has been an unqualified success in the selected military recruit population for which it was intended. A live, attenuated rubella (German measles) vaccine for prevention of birth defects by vaccination of women, before child-bearing age, has great promise and is almost ready for the relatively large-scale evaluation trials required before licensing for production.

A vaccine against the mycoplasma (a kind of naked bacteria), responsible for a considerable amount of pneumonia in the young, has been developed in the laboratory, and has real promise as a practical measure. On the other hand, attempted development of vaccines for respiratory syncytial and parainfluenza virus infections (significant causes of death in infants) has revealed crucial and previously unsuspected problems in what determines the immunity to disease and its course. Influenza, an enemy well-known for fifty years, still has its mysteries. The current vaccine is of less than desirable efficacy, and its use in the face of an epidemic presents serious technical and logistical problems. In recent outbreaks, even the isolation of the virus has proved difficult, and it has become obvious that much remains to be learned about the protein protective substances in the blood and other body fluids (antibodies) that determine immunity.

Bacterial pneumonia is still a major cause of death, especially in the aged. Contrary to the generally-held opinion, antibiotic therapy is not successful in preventing all deaths, especially those that occur soon after onset. The production of an efficient vaccine against the eight or ten most important types of pneumococcus that account for 70-75% of deaths appears to be technically feasible. Clinical evaluation will be made to determine the practical usefulness of such a vaccine.

National Institute of Allergy and Infectious Diseases

EMPHYSEMA AND CHRONIC OBSTRUCTIVE LUNG DISEASE
(Amounts in thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Grants | 945 | 1,013 | 1,050 | 1,150 | 1,200 | 1,300 | 1,400 | 1,500 |
| Direct Operations | | | | | | | | |
| In House | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Contract | 0 | 0 | 0 | 500 | 1,000 | 1,500 | 1,500 | 1,500 |
| TOTAL | 945 | 1,013 | 1,050 | 1,650 | 2,200 | 2,800 | 2,900 | 3,000 |
| No. of Positions | 0 | 0 | 0 | 4 | 6 | 6 | 6 | 6 |

Emphysema and the associated chronic obstructive diseases of the lung are a current serious public health problem that is sharply increasing in importance. There were about 26,000 deaths in 1965 and the death rate has been doubling about every five years. Death is only part of the story. It is estimated that emphysema disables one out of every 14 wage-earners over 45 years old, and it is second only to heart disease in the cost for disability allowances. Although much can be done to temporarily alleviate distress, there is no cure and no real understanding of causation or how the disease progresses.

Regardless of the sums spent on rehabilitation and disability payments, this dreary picture is not likely to change until more research opportunities are uncovered. The difficulty in increasing the research effort stems not from a failure to appreciate the importance of the disease complex, but rather--in the judgment of the research community--the lack of obvious opportunities to exploit.

Until an acceptable animal model system for emphysema is discovered, research, necessarily based on human observation, will be slow, long-term, and difficult to interpret. An emphysema-like condition is found naturally in horses (heaves) and can be induced chemically in dogs and mice. All of these species are under intensive study.

Human emphysema, however, is almost certainly not caused by any single substance or microbial agent. Many influences--smoking, the repeated insults of bacterial and viral infections, air pollution, sex, race, and physical fitness--appear to act together to influence the frequency or extent of emphysema. This complex causation and the slow, insidious onset make the disease best studied in medical centers well equipped to bring the various medical disciplines to bear. Experience at such a center over the last 11 years suggests that deaths from emphysema and chronic bronchitis may be under-reported by at least one-half. Other centers are studying selected populations over the long term, using a variety of pulmonary function tests and intensive bacterial and virological testing. Still other laboratories are concerned with the more detailed investigation of the physiology, immunology, and function of specific structures in the airways--the alveoli, the cilia, mucous-producing and other specialized cells--that appear to play a significant role in the disease. All of these studies should be intensified and expanded in scope.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

AUTOMATED CLINICAL LABORATORIES

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $1,400 | $1,400 | $1,600 | $2,000 | $2,200 | $2,500 | $3,000 | $3,500 |
| Direct Operations: | | | | | | | | |
| Contracts..... | 348 | 500 | 500 | 1,500 | 2,000 | 4,000 | 6,000 | 10,000 |
| Total..... | 1,748 | 1,900 | 2,100 | 3,500 | 4,200 | 6,500 | 9,000 | 13,500 |

A few years ago the average hospital laboratory was able to perform some eight to ten clinical analyses. Today physicians require several hundred different tests which employ complex and sophisticated analytical techniques so that the laboratories are faced with an enormous and rapidly growing task.

The successful diagnosis and treatment of catastrophic medical events may depend upon rapid and accurate laboratory analyses which were not available a few years ago. The growing complexity of the analytical procedures requires highly trained technical personnel which is both expensive and in long-term short supply. Health authorities universally agree that a solution to this problem is to automate the clinical diagnostic laboratory.

Automated clinical laboratories now evolving under the Institute's program are of a modular nature structured to benefit all sizes of hospitals, from the small community hospital to the large university hospital complex. The program is oriented towards the development of automated clinical laboratories which may result in lower costs to the patient through lower laboratory fees and better medical care. Laboratory analyses will be more accurate and much faster with little increase in personnel demands. The development of such a program demands very precise control of rapidly developing technology and will therefore be conducted largely through the contract mechanism. However, an ongoing and slowly expanding grants program is necessary to provide basic concepts to be exploited in the contract area.

In this country in most advanced laboratories there is still less than 50 percent automation in any area. By sequentially improving both the hardware and software now available, it should be possible to increase automation levels 15 to 20% within 3-5 years.

The Institute has been making steady progress in the development of automated methods for analysis of urinary constituents and drugs, and the identification of pathogenic bacteria. Major developments are directed toward computer integration with automated methods and with improvement of sensors for the detection of specific body constituents. We would estimate that $2 million could be spent profitably in this area in 1970 with gradually escalating amounts over the next few years.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

PHARMACOLOGY-TOXICOLOGY

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $5,324 | $6,000 | $6,500 | $7,200 | $8,000 | $9,000 | $10,000 | $11,000 |
| Direct Operations: | | | | | | | | |
| Contracts..... | 800 | 1,000 | 1,000 | 2,000 | 4,000 | 6,000 | 12,000 | 20,000 |
| Total..... | 6,124 | 7,000 | 7,500 | 9,200 | 12,000 | 15,000 | 22,000 | 31,000 |

This Institute has a specific mission to develop a strong scientific base for the design and rational use of new and more effective drugs and to develop a greater understanding for why many drugs and chemicals are toxic to man.

Effective drugs in only a few years have altered the course of many diseases. Such gains are deceptive because they tend to suggest that we have solved most of our serious disease problems. It should be noted that cancer, heart disease, rheumatoid arthritis, and other chronic diseases are still inadequately treated with presently available drugs.

Serious problems develop in the use of drugs which are unrelated to the disease under treatment. Genetic constitution varies greatly from one individual to another and may cause unforeseen difficulties and variability in response to drugs. More than ten percent of the population is allergic or hypersensitive to one or more of the 500 most commonly used medications. The little now known about toxic effects of long term exposure to drugs and chemicals is enough to cause gravest concern among public health authorities. We must obtain this information in the shortest possible time as the potential for very real harm to significant numbers of people clearly exists. The pharmacology-toxicology program of the Institute is making a determined effort to seek solutions to these problems.

Observable trends in classical pharmacology departments will not contribute strongly to the broad health aims of this program. Carefully planned centers are needed and these operate best under contract. Experience has indicated that such programs should be started with relatively small program projects and later converted into contract operation as soon as a broad capability has been established. Many of the ten program projects now in operation will serve as nuclei for future centers. A full scale center operated by contract will require $2-4 million per year.

During the 1970-74 period the development of the pharmacology-toxicology program will continue with the establishment of new centers on as wide a geographical base as possible. Among the problems to be attacked will be the influence of the genetic makeup of an individual on his response to drugs, the effects of common materials or chemicals (such as tobacco) on response to drugs, and a rapid development of our program in clinical pharmacology.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

ANESTHESIOLOGY

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $2,926 | $3,500 | $4,000 | $5,000 | $6,100 | $7,400 | $8,900 | $10,600 |
| Direct Operations: | | | | | | | | |
| Contracts..... | --- | --- | --- | --- | --- | --- | --- | --- |
| Total..... | 2,926 | 3,500 | 4,000 | 5,000 | 6,100 | 7,400 | 8,900 | 10,600 |

Anesthesiology is the one science upon which all surgery relies. Millions of patients are placed under general anesthetics each year and the cost of their medical care, the length of hospital stay, and the rapidity of recovery from surgery is dependent to a large extent upon the efficacy, and rate of elimination of the anesthetic. We must not only develop new anesthetics with ideal properties of muscle relaxation, depth of anesthesia, and speed of recovery, we must also understand the mode of action of presently available anesthetics and learn more about their toxicity. Research into these problems has been stimulated by NIGMS through the development of four centers.

The first of these was an award to the University of Pennsylvania, culminating more than two decades of anesthesiology research and training under Dr. Robert Dripps. Here research on man and animals will determine the effects of widely used anesthetics on cells and tissues of the body. At Columbia University a center has been established under the direction of Dr. E. M. Papper through the careful combination and coordination of several research projects supported by NIGMS for the past six years. This center is investigating problems in obstetrical anesthesia and physiology of the new born, the pharmacological basis of anesthesia, and the effects of anesthetics on the respiratory and cardiovascular system. A center is also being established at Harvard Medical School under Dr. Henry Bendixen envolving several major hospitals in the Boston area and at Northwestern University staff and facilities are being assembled by Dr. James Eckenhoff to systematicallyassess monitoring devices for use in the anesthetized patient.

These four centers have been developed as a direct result of the $1 million appropriated by Congress for this specific purpose. We now have approved applications for additional centers which will afford a wider geographical distribution. One of these applications at the University of Washington will be concerned with automation of anesthetic procedures to reduce the need for trained anesthetists.

Additional centers for research and training in this vital area should be established in future years.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

RADIOLOGY

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $286 | $500 | $750 | $1,800 | $2,600 | $3,400 | $4,400 | $5,400 |
| Direct Operations: | | | | | | | | |
| Contracts..... | --- | --- | --- | 1,000 | 1,300 | 1,500 | 2,000 | 2,500 |
| Total..... | 286 | 500 | 750 | 2,800 | 3,900 | 4,900 | 6,400 | 7,900 |

Radiographic techniques constitute vital tools for assessing the damage, determining the appropriate treatment, and measuring the success of therapy in most major disease entities including coronary artery disease, cancer, and stroke. Progress in nearly all areas of clinical medicine in recent years has been accompanied by an exponential increase in the need for existing types of radiodiagnostic aides and has demonstrated the need for completely new techniques--most of which are within the present state-of-the-art. It has become essential that the search for improved diagnostic methods concentrate on the engineering development of systems to increase the productiveness of practicing radiologists.

Pursuing these opportunities, the Institute recently awarded a grant to the University of Pittsburg to develop and clinically evaluate electronic techniques for recording, reviewing, and storing most types of radiographic images. Successful accomplishment of this proposal, under the direction of Dr. Ernest Sternglass, will have a profound impact on radiology.

The radiology research program in the National Institute of General Medical Sciences is just beginning to develop. A few grants concerned largely with the development of new techniques, autoradiography, new contrast materials, three-dimensional imaging of X-rays, and the automated reading and storing of X-ray pictures are in operation. Though few in number, they represent the extent of the field. Because of the slow research development in this field, centers have as yet not been established. We would anticipate the first of these centers in 1970. Research in X-ray methodology is an extremely extensive process because of the massive equipment required. Increases in funds could aid materially in the development of the field which otherwise will lag for years. Special funds have been authorized by Congress to develop diagnostic radiology centers, and these must be complemented by a strong contract program for development of equipment. Research grants must continue to develop a strong theoretical base concentrating on the use of new forms of energy (i.e., sound) for visualization.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

TRAUMA

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $2,435 | $3,000 | $3,500 | $4,000 | $4,500 | $5,000 | $5,500 | $6,000 |
| Direct Operations: | | | | | | | | |
| Contracts..... | --- | --- | --- | --- | --- | --- | --- | --- |
| Total..... | 2,435 | 3,000 | 3,500 | 4,000 | 4,500 | 5,000 | 5,500 | 6,000 |

Death from traumatic injury in the United States is a disease epidemic in the truest sense of the word. Motor vehicle accidents are the leading single cause of accidental death; they account for about 40,000 deaths per year; 60,000 lives are lost from other kinds of accidents.

For several years the National Institute of General Medical Sciences has supported research in trauma to develop new life-saving techniques and methods of therapy. We have found the best research approach in trauma to be multidisciplinary teams of investigators working in specialized centers having laboratory and intensive patient care facilities. The Institute established and now supports six of these special trauma research centers with grants totaling more than $1 million.

The six operating centers for trauma research are concerned with a wide variety of problems yet these encompass only a small fraction of the effort needed. It is necessary to develop a regional distribution of trauma research centers together with supporting clinical facilities. The Institute could profitably spend about $4.0 million in 1970 for operation of research centers.

It has been estimated that a reduction of 5 percent in the effects of trauma could save the economy hundreds of millions of dollars per year in lost wages, hospital care, and rehabilitation costs.

Both the National Institute of General Medical Sciences and the National Institute of Neurological Diseases and Blindness have responsibilities in the field of trauma. The NINDB has been specifically assigned a role in the treatment and assessment of head injury while NIGMS is concerned with injury to other areas of the body. The two programs are working in cooperation with each other in the exchange of information and in actual joint funding of trauma centers wherever appropriate. Such cooperation will be extended in the future.

A program in trauma requires a cadre of surgeons trained in the specialized treatment of trauma patients. Many young surgeons are now returning from Viet Nam with considerable experience in this area. Means must be provided to attract the best of these individuals into research and teaching careers utilizing their knowledge of trauma developed in these research centers.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

BEHAVIORAL SCIENCES

(In Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | $550 | $634 | $700 | $2,000 | $2,500 | $3,000 | $3,500 | $4,000 |
| Direct Operations: | | | | | | | | |
| Contracts..... | --- | --- | --- | --- | 1,000 | 2,000 | 3,000 | 4,000 |
| Total..... | 550 | 634 | 700 | 2,000 | 3,500 | 5,000 | 6,500 | 8,000 |

The NIH has presented to Congress a report on the fundamental importance of the behavioral sciences in the study and understanding of disease and the maintenance of health. NIGMS has been assigned a key role in the development of these sciences. The Institute is particularly interested in the development of more precise quantitative methods for the study of behavior. Man must understand, to the greatest possible extent, how he thinks, relates to his fellow man, and integrates with society as a whole. In each of these areas attempts must be made to provide quantitation through the development of new instrumentation and the use of the newer technologies such as the computer sciences.

The proposed program will support a planned start in the broad field of the behavioral sciences. It is apparent that the development of a strong data base and a large scale program encompassing fundamental research in psychology, sociology, and anthropology will depend upon increases in support. To adequately fund the program we estimate that approximately $2 million will be necessary in 1970 with gradually increasing funds during the next three or four years.

Because of the relatively small research base in NIGMS at the present it is difficult to predict the exact directions in which the behavioral sciences will move in the next few years. The NIGMS proposes, therefore, a continual assessment of the field, its development and health and will judiciously use contract funds as we identify areas in which a coordinated program is possible. Such coordination may take the form of large scale centers funded through contracts placed in close apposition to our excellent training programs in the field. Such centers would cost about $1 million per year each to operate and we would hope to have four in operation by 1974.

National Institute of Child Health and Human Development

INFANT MORTALITY

(Dollar amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | 9,070 | 9,268 | 9,268 | 10,118 | 10,500 | 12,100 | 13,800 | 15,400 |
| Direct Operations: | | | | | | | | |
| In House..... | 100 | 200 | 250 | 250 | 300 | 375 | 400 | 425 |
| Contracts..... | 246 | 321 | 371 | 1,021 | 1,200 | 1,400 | 1,500 | 1,700 |
| Total | 9,416 | 9,789 | 9,889 | 11,389 | 12,000 | 13,875 | 15,700 | 17,525 |
| Related Grants..... | -- | -- | xx | xx | xx | xx | xx | xx |
| No. of positions... | 7 | 14 | 17 | 17 | 20 | 25 | 27 | 28 |

One of the most pressing health problems in the United States today is its high infant mortality rate. In 1967, the infant mortality rate for the United States was 22.1 per 1,000 live births, placing it thirteenth among the countries of the world. Eight percent of live born infants are classified as premature, and these account for almost 60% of all infant deaths. The most frequent cause of death among premature infants is the respiratory distress syndrome. Were prematurity to be abolished, the current 78,200 infant deaths per year would be reduced by an estimated 33,000.

Too little is known about what causes, or how to prevent prematurity or the respiratory distress syndrome (RDS), for which, so far, no specific method of treatment has proven effective. There are a number of impediments of progress in these areas: 1) gaps in scientific knowledge, especially concerning the pathogenesis of prematurity and RDS; 2) since RDS is not precisely defined, there is little useful and comparable data concerning RDS; 3) manpower; 4) problems of ethics and informed consent; 5) gaps in communication; and 6) lack of necessary specialized facilities. In FY 1970 1.5 million dollars are needed over the 1969 budget for Federally Directed Research to: 1) establish a coordinated maternal-infant clinical research center with inpatient and out-patient components to follow high risk pregnancies through the neonatal period developing criteria for the early detection, prevention, and management of prematurity and RDS-$600,000; 2) contract for animal research in the production and prevention of premature births -- $150,000 ; 3) contract for collaborative epidemiologic studies of a large population to obtain better data leading to the establishment of standard criteria for diagnosis of DRS, for documenting high-risk pregnancies, and for the development and demonstration of better regimens of early management of the high-risk fetus and newborn--$350,000; 4) contract for collaborative studies in the treatment of RDS (controlled comparison of techniques) including the research and development of new equipment to better monitor physiologic paramenters -- $150,000; for Investigator Directed Research, to fund additional approved research applications concerned with nutritional, endocrinological and genetic factors as they relate to prematurity and RDS, as well as studies of uterine blood flow and fetal blood supply, factors causing relationship to RDS and prematurity, environmental factors, etc.--$250,000.

By these measures it is expected that in 1974, although all answers to prematurity and RDS will not be known, means to reduce sharply not only the mortality but also the long term disabling sequelae will be demonstrable. This should include establishment of an effective mode of treatment of RDS as well as prevention of its occurrence and effective methods of controlling it while it is still in a mild stage.

National Institute of Child Health and Human Development

POPULATION RESEARCH

(Dollar amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants..... | 4,171 | 4,442 | 4,550 | 8,500 | 10,000 | 11,800 | 13,600 | 15,900 |
| Direct Operations: | | | | | | | | |
| In House..... | 554 | 705 | 826 | 1,000 | 1,100 | 1,300 | 1,500 | 1,700 |
| Contracts..... | 1,210 | 1,235 | 4,735 | 8,000 | 9,200 | 10,700 | 12,200 | 14,100 |
| Total ..... | 5,935 | 6,382 | 10,111 | 17,500 | 20,300 | 23,800 | 27,300 | 31,700 |
| Related Grants..... | -- | -- | xx | xx | xx | xx | xx | xx |
| No. of positions | 43 | 54 | 74 | 77 | 85 | 100 | 115 | 131 |

The Scientific Problem

The stresses and strains of excess population growth are visible throughout the world and give evidence to the fundamental difficulties which this and other countries will face unless all appropriate means to diminish the increasing disproportion between excess fertility and resources are employed.

Population research must be responsive to all the issues involved, both biological and social. NICHD, accordingly, is organizing a research program 1) to develop and evaluate contraceptive methods, and 2) to investigate the complex social, psychological, and economic factors which are operative.

The primary effort is in contraceptive development and evaluation. Intrauterine contraceptive devices and oral contraceptives are important innovations in contraceptive technology but do not fully satisfy all the criteria established for the ideal contraceptive method, which are effectiveness, safety, low cost, reversibility, and acceptability to all groups. Since no one method is likely to fulfill these criteria, our goal is the identification of areas where research is on the threshold of acquiring fundamental information which is likely to lead to the rapid development of an array of new contraceptive methods that can be fitted to the diverse, medical, social and psychological needs of various populations.

Recent Accomplishments

The principal effort has been on studies of the mechanism of action and medical effects of oral contraceptives and intrauterine devices. An important goal of these studies is the elucidation of the mechanism of action of these and other contraceptives so that it may be possible to design safer, more efficient and more effective contraceptive techniques.

With the advice and assistance of the Population Research Advisory Committee the Institute is planning an organized program of research leading to the development of new contraceptive methods. The Institute will support through contract several clusters of contracts on topics which seem most likely to produce significant technological improvements. Several examples include: 1) studies of the corpus luteum, with the intent of developing a luteolytic agent, 2) sperm capacitation and seminal fluid composition, leading to better male contraceptives, and 3) studies of the local events at ovulation, to improve the means to practice periodic abstinence.

National Institute of Child Health and Human Development

PSYCHO-SOCIAL DEPRIVATION, EARLY COGNITIVE DEVELOPMENT

(Dollar amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants | 7,985 | 8,371 | 9,287 | 9,700 | 12,270 | 15,335 | 19,170 | 24,900 |
| Direct Operations: | | | | | | | | |
| In House..... | 539 | 562 | 623 | 750 | 930 | 1,165 | 1,460 | 1,600 |
| Contracts..... | 961 | 1,000 | 1,110 | 2,250 | 2,800 | 3,500 | 4,370 | 4,500 |
| Total | 9,485 | 9,933 | 11,020 | 12,700 | 16,000 | 20,000 | 25,000 | 31,000 |
| Related Grants..... | | | xx | xx | xx | xx | xx | xx |
| No. of positions... | 36 | 37 | 42 | 50 | 62 | 78 | 97 | 107 |

(Dollar amounts and positions relate to entire Behavioral Sciences Activity)

Psycho-social deprivation is an area of primary relevance to the basic research mission of NICHD. Of singular importance is the impact of impoverished environments on development throughout the life span.

Central to the issue is the isolation of those significant developmental factors - occurring during critical periods in infancy and early childhood - that differentiate those children who function significantly below their apparent capacity from the children who function at or near their optimum level. For example, which specific deleterious factors cause a disadvantaged child - tested and rated normal at birth and early infancy - to have become a "retarded" individual by the third or fourth year of life. Preliminary findings indicate that some of the etiological factors may be found in the nature of the relationship between the infant-preschool child and his caretaker(s).

Since there is increasing evidence that the critical period for cognitive development is in infancy and the preschool years, basic research is needed to identify the etiological factors underlying personal-social and cognitive deficits and to experiment with ways to reverse the regressive effects of early deprivation. The focus of Federally directed systematic investigations should be: (1) to define with great precision the characteristics of depriving environments during infancy and preschool years; (2) to study the process of reversing or ameliorating the impact of deprivation by experimenting with systematically, varied aspects of early experience; and (3) to analyze systematically various types of preschool programs designed to counteract early deprivation. Such a research effort would provide more precise understanding of the factors that facilitate and those which impede intellectual and personal-social development.

Although the impetus in this area comes from legitimate concern with the disadvantaged segment of society, fundamental understandings of the developmental process that may accrue are relevant to and span the total breadth of society. In addition, these theoretical issues have acquired primary importance as social action programs attempt to apply fragmentary knowledge to preventive and ameliorative programs for young children. The accelerating trend to establish such programs with too little understanding of bio-behavioral phenomena appears to represent a monetary and human cost to society in excess of that expected, were the programs undergirded by a more adequate knowledge base.

Recent Accomplishments

Currently, NICHD has ongoing intramural, contract, and extramural projects involved in basic research in this area. In addition, task forces are being organized to address the psycho-social deprivation issues and to prepare definitive papers. These papers will provide directions for expanding the extramural and intramural research and contract programs.

National Institute of Child Health and Human Development

GERONTOLOGY RESEARCH CENTER

(Dollar amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | -- | -- | -- | -- | -- | -- | -- | -- |
| Direct Operations: | | | | | | | | |
| In House..... | 1,716 | 1,600 | 2,500 | 3,525 | 4,023 | 4,425 | 4,025 | 4,025 |
| Contracts..... | -- | -- | -- | -- | -- | -- | -- | -- |
| Total | 1,716 | 1,600 | 2,500 | 3,525 | 4,023 | 4,425 | 4,025 | 4,025 |
| Related Grants..... | -- | -- | xx | xx | xx | xx | xx | xx |
| No. of positions... | 115 | 140 | 180 | 230 | 270 | 300 | 300 | 300 |

The Scientific Problem

The intramural research for the Adult Development and Aging Program is focused upon: 1) the description of age differences and age changes in biochemical, biophysical, physiological, and behavioral characteristics; and 2) the explanation of these age changes at the fundamental level of cellular and molecular processes.

The repeatedly expressed concern of Congress and the pressure from the citizens for a more vigorous research program in aging will not be met if funds for the expansion of research and research training are not available to permit utilization of the facilities created. Information is needed in the morphological area to better understand the observations in current studies. The field is now ready for vigorously studying the aging process at the cellular level in tissue culture.

Recent Accomplishments

Facilities: The 90,000 square foot building, located in Baltimore, for fundamental research in aging was ready for occupancy on March 1, 1968. There are 130 on the staff now; full complement is estimated to be 300.

Research: In the past year an unexpected finding in pulmonary and muscular systems research demonstrated that performance of the two systems declined more with age than did the performance of the individual components.

National Institute of Child Health and Human Development

MENTAL RETARDATION RESEARCH CENTERS

(Dollar amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | -- | -- | 2,000 | 7,300 | 13,000 | 19,500 | 22,700 | 25,000 |
| Direct Operations: | | | | | | | | |
| In House..... | -- | -- | -- | -- | -- | -- | -- | -- |
| Contracts..... | -- | -- | -- | -- | -- | -- | -- | -- |
| Total | -- | -- | 2,000 | 7,300 | 13,000 | 19,500 | 22,700 | 25,000 |
| Related Grants..... | -- | -- | xx | xx | xx | xx | xx | xx |
| No. of positions... | -- | -- | -- | -- | -- | -- | -- | -- |

The Scientific Problem

To augment the research attack on the cause, prevention, diagnosis, amelioration, and treatment of mental retardation, a number of research centers were authorized by Congress. The primary objective of these facilities is to provide a comprehensive and cohesive program of research and research training in the multidimensional aspects of mental retardation. (Each center program includes representation from many university departments and a wide range of biomedical, behavioral, and social scientists.) Funds for programmed research are needed to help each center accomplish its basic, long-term (20 years) mission by strengthening center administration, adding essential research strength in gap areas of center programs, providing core scientific equipment for center-wide use, and for translating research findings to service; and, among others, for major program projects to improve methods of early diagnosis, develop means for preventing prematurity and high-risk births, understand genetically based retardation, and to develop means for combating retardation consequent to depriving life circumstances and aberrant child rearing practices. In addition, funds are needed to support needed training of scientific personnel in new programs made possible by the centers. If research and training funds are not available in the above amounts, the primary purpose for constructing these facilities will not be realized and they will be underutilized or used for other purposes.

Recent Accomplishments

By June 30, 1967, construction grant awards had been made to twelve institutions under the provisions of Public Law 88-164 which authorized the construction of centers for research on mental retardation and related aspects of human development.

Six of the centers will be operational by the close of 1968, two more in 1969, a total of eleven in 1970, and all twelve in 1971. Within two years after construction, the average annual budget per center is estimated at $2,600,000.

Division of Environmental Health Sciences

NATURAL PRODUCTS

(Amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | $254 | $325 | $390 | $542 | $800 | $1,076 | $1,499 | $1,773 |
| Direct Operations: | | | | | | | | |
| Inhouse..... | --- | 260 | 650 | 1,136 | 1,340 | 1,405 | 1,640 | 1,859 |
| Contracts..... | --- | --- | --- | 550 | 1,100 | 1,650 | 2,480 | 3,550 |
| Total..... | 254 | 585 | 1,040 | 2,228 | 3,240 | 4,131 | 5,619 | 7,182 |
| Positions..... | --- | 13 | 38 | 66 | 78 | 82 | 96 | 109 |

Botanical substances, microbiological agents, and other natural products can adversely affect as well as benefit health. The toxicity for man of such botanical substances as certain alkaloids and cycad nuts is well known and recently it has been demonstrated that certain metabolites of the common mold Aspergillus flavus are extremely toxic to a wide variety of animal species. Fungal contamination of food in this and related organisms has been shown to exist in foods now consumed by a large segment of the population. Their widespread distribution as contaminants makes this a matter of serious public health concern. The National Cancer Institute, through its contract support to the Massachusetts Institute of Technology, was responsible for the isolation, purification, and structural identification of aflatoxins, the toxic metabolites of A. flavus. Currently funds support research for the synthesis of these toxic compounds in both the unlabeled and isotopically labeled forms. The toxicity of other mold products is particularly in need of investigation at this time inasmuch as epidemiological studies have identified correlations between liver disease in man and marked presence of these substances as food contaminants in high endemic areas. The passage of these toxic substances through the milk creates a specific problem because of the susceptibility of the newborn to the action of toxic agents.

Mold contamination of foods is widespread in the United States, and the unprecedented potency of aflatoxin strongly suggests that minimal concentrations may adversely affect those exposed. This appears to be particularly true under conditions of sub-standard nutrition or antecedent or concurrent disease of anatomic target sites. The development of sophisticated instrumentation including Nuclear Magnetic Resonance, Electron Spin Resonance, gas chromatography, mass spectrometry, and activation analysis now permits microquantification of these agents and their products in environmental sites of food and water as well as allow studies on the correlation of their toxicity with their anatomic and metabolic fate. A vigorous program is now possible utilizing the instrumentation described and current advanced methods for in vitro and in vivo bioassay.

Public health preventive measures aimed at eliminating these agents from the environment would require an effort of monumental proportions. It is therefore imperative that an environmental and biological profiling of mycotoxins and other natural products be undertaken with dispatch for the purpose of specifically identifying those in need of elimination from water and food used for domestic animals and human consumption.

The Division, through a combined chemical and biological approach to the problem correlated with field studies in collaboration with other Federal agencies can contribute to a firmer understanding of the magnitude of the hazard as well as direct to possible protective measures.

Division of Environmental Health Sciences

SMOKING AND HEALTH

(Amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | --- | $82 | $92 | $300 | $330 | $380 | $455 | $510 |
| Direct Operations: | | | | | | | | |
| Inhouse..... | --- | --- | 40 | 250 | 265 | 270 | 288 | 305 |
| Contracts..... | $100 | 200 | --- | 600 | 1,200 | 1,800 | 2,700 | 3,950 |
| Total..... | 100 | 282 | 132 | 1,150 | 1,795 | 2,450 | 3,443 | 4,765 |
| Positions..... | --- | --- | 4 | 14 | 15 | 15 | 16 | 17 |

Epidemiological and clinical studies have established that a history of prolonged cigarette smoking is associated with an increased risk of chronic, obstructive, and degenerative pulmonary disease, (emphysema, bronchitis, and fibrosis), as well as of neoplastic disease. Analytical studies have established the presence of numerous pulmonary irritants in cigarette smoke aerosols and clinical and laboratory studies have demonstrated alterations in pulmonary function as well as an adverse affect of cigarette smoke on the normal muco-ciliary apparatus of the lung. There exists a great need to elucidate the pathogenesis of bronchitis and emphysema, two diseases of non-specific origin.

Within the recent past, important advances have been made in understanding the cellular synthesis of alveolar surfactant as well as its chemical and physical properties. Alterations of this substance in response to irritants have been only superficially investigated. Similarly recent advances in the study of pulmonary elastic tissue, including biochemical studies concerned with the maintenance of its integrity, suggest guidelines for future studies. Increasing the depth of our knowledge of surfactant physiology and elastic tissue biology should contribute to our understanding of the origin and progression of emphysema.

Total body exposure chambers planned for the Division and the competency of its staff in aerosol synthesis and maintenance under the most sophisticated conditions of control will permit the development of animal model systems for exposure under circumstances essentially simulating those of human exposure. Lack of these facilities and appropriate staff has until recently been a major impediment in achieving further advances in the study of degenerative pulmonary diseases.

Chronic bronchitis and interstitial pneumonitis are ill defined entities. However, recent studies of bronchial mucus production in health and disease as well as growing understanding of chronic interstitial disease of the lung now permit an approach to the identifying mechanisms of pulmonary fibrosis and alveolar vascular disease. The ability to expose a spectrum of mammalian species to irritant aerosols of environmental importance will permit a coordinated approach for the study of the individual disease entitites described as well as the identification of possible inter-relationships.

Division of Environmental Health Sciences

ENVIRONMENTAL HEALTH SCIENCES INSTITUTES

(Amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants.. | $2,529 | $3,000 | $3,000 | $3,700 | $4,500 | $5,300 | $6,200 | $7,300 |

The university-based center provides a framework in which a broad spectrum of research can be integrated and brought to bear on problems of environmental health. There is no single model for organizing a center. Each develops as an outgrowth of a university's particular resources and strengths and partially in response to specialized problems encountered in the locality. By serving as sources of information to health departments on the application of scientific findings to the solution of local problems, they have a considerable impact on the quality of environmental research and practice in the surrounding area.

The center also furnishes a structure for graduate training of excellence and provides advance training in a depth that is available in few other places. A most pressing need for the future of research in environmental health is the provision for attractive, stable career opportunities. Centers make such opportunities available not only for those already in biomedical research, but as a means of attracting promising young people into the field. By contrast, the present pattern of university training is unlikely in the immediate future to produce a corps of scientists with a primary commitment to environmental health.

Centers cannot effectively embrace more than a few aspects of this broad and complex field. Accordingly, they differ markedly in their orientation and program priorities. Individual centers may emphasize such program areas as environmental carcinogenesis, natural biological systems, pesticide biology, etc. Effective utilization of these facilities requires the existence of a resource, such as the National Environmental Health Sciences Center that can identify mission-oriented problems, formulate objectives, and implement program efforts in a centrally coordinated manner. The NEHSC is planned to have a problem-solving competence and depth that will permit evaluation, review, and the maintenance of close working relationships with these external programs.

The National Environmental Health Sciences Center will not attain a scope and size sufficient to investigate more than a portion of the key environmental health problems. Consequently, a sufficient number of new centers must be developed to insure a balanced national program. Starting with the existing base, there is a projected need for 11 additional centers in order to achieve minimal coverage of the major problem areas, as well as a uniform distribution of resources to help meet regional environmental health problems. To reach this goal in 1974 would necessitate an increase in the annual funding level from the current $3.0 million to $7.3 million and a net gain of two centers per year specializing in such needed areas as chemical mutagenesis, food toxicology, research on heavy metals, and synergistic pharmacology.

Division of Environmental Health Sciences

RESEARCH ON THE PULMONARY EFFECTS OF ALPHA EMITTERS

(Amounts in Thousands)

| | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 |
|---|---|---|---|---|---|---|---|---|
| Research Grants... | --- | --- | $100 | $100 | $200 | $300 | $450 | $500 |
| Direct Operations: | | | | | | | | |
| Inhouse..... | --- | --- | 100 | 331 | 335 | 345 | 360 | 425 |
| Contracts..... | --- | $200 | 350 | 350 | 500 | 500 | 500 | 500 |
| Total..... | --- | 200 | 550 | 781 | 1,035 | 1,145 | 1,310 | 1,425 |
| Positions..... | --- | --- | 5 | 12 | 14 | 18 | 20 | 25 |

Miners of uranium ores have an increased risk to the development of lung cancer as a result of their breathing air containing radon and its radioactive decay products. Several studies indicate that other environmental factors may contribute to this enhanced risk.

The scientific criteria for the establishment of control standards in uranium ore miners for the protection of miners should be improved. Combined laboratory, clinical, and epidemiological studies for the determination of dose response relationships in the development of lung cancer during exposure to alpha emitters are urgently needed. Highly sensitive whole body counters are available for more accurate measurement of body burden of radioactive material.

Exposure of experimental animals to radon and its daughters alone and in combination with other environmental agents under controlled conditions is an urgent necessity. Appropriately designed protocols should include variations in dosage of alpha emitters, vehicles for these emitters, and other factors including hydrocarbons, oxides of nitrogen, hard rock particles, and cigarette smoke.

It is planned to expand the current epidemiology studies from the current 5,000 miners under study to include the approximately 20,000 miners known or believed to have received significant exposure to alpha emitters in the past.

Research to facilitate early diagnosis by exfoliative cytology and broadened studies on the pathogenesis, morphogenesis, and morphology of lung cancer in uranium miners is necessary. The former should include determination of the actual range of alpha particles and tissues, the variations in the thickness of the bronchial, epithelium, the role of delta rays, and the effect of environmental co-factors. The increase in pulmonary cancer in uranium miners appears to be associated with approximately a 1,000 Working Level Month dose with ten years of underground exposure. While positive assurance that a "practical" threshold limit for exposure to airborne alpha emitters cannot be given at present, the long induction period (5 to 20 years for lung cancer) and the modifying effect of age of the miner at onset of exposure suggests the possibility that a "practical" threshold may be identified.

DIVISION OF RESEARCH FACILITIES AND RESOURCES
PHARMACOLOGY-TOXICOLOGY INFORMATION
(Dollars in thousands)

| | F.Y. 1967 | F.Y. 1968 | F.Y. 1969 | F.Y. 1970 | F.Y. 1971 | F.Y. 1972 | F.Y. 1973 | F.Y. 1974 |
|---|---|---|---|---|---|---|---|---|
| Direct operations: | | | | | | | | |
| Inhouse | $60 | $60 | $60 | $105 | $140 | $175 | $210 | $245 |
| Contracts | 392 | 1,500 | 1,500 | 1,600 | 2,000 | 2,700 | 3,500 | 4,500 |
| Total | 452 | 1,560 | 1,560 | 1,705 | 2,140 | 2,875 | 3,710 | 4,745 |
| Positions | 2 | 2 | 2 | 3 | 4 | 5 | 6 | 7 |

The Information/Communications Component of the NIH Pharmacology-Toxicology Program has two basic objectives: (a) the development and evaluation of computer-based techniques for interactive handling of data relevant to molecular structure/biological activity relationships and (b) the provision of services of such information science technology in support of pharmacology-toxicology research.

The major element in this program is a collaborative project in computer system development and application involving the Division of Research Facilities and Resources (DRFR) and the Division of Computer Research and Technology (DCRT). Once a basic general research support computer capability has been implemented at DCRT (partially by DCRT staff and partially by extramural organizations under contract to DRFR) remote terminals will be made available to investigators throughout the Nation for the purpose of system evaluation and for applications in research. It is anticipated that such an information system would be an invaluable research tool in unravelling the mechanisms of action of therapeutic agents, hormones, and toxic substances. In addition to the DRFR/DCRT collaborative project, this program will continue to support specific projects involving development of new information-handling techniques and compilation of data bases with extramural organizations.

It is imperative that computer based information-handling capability for pharmacology-toxicology be accelerated to gain new knowledge into the mechanisms of action of chemical compounds in living systems.

DIVISION OF RESEARCH FACILITIES AND RESOURCES
COMPUTER RESOURCES
(Dollars in thousands)

| | F.Y. 1967 | F.Y. 1968 | F.Y. 1969 | F.Y. 1970 | F.Y. 1971 | F.Y. 1972 | F.Y. 1973 | F.Y. 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants | $8,562 | $9,600 | $9,900 | $12,000 | $14,400 | $17,200 | $20,500 | $24,700 |
| Direct operations: | | | | | | | | |
| Inhouse | 130 | 152 | 198 | 252 | 303 | 367 | 431 | 510 |
| Total | 8,692 | 9,752 | 10,098 | 12,252 | 14,703 | 17,567 | 20,931 | 25,210 |
| Positions | 9 | 10 | 13 | 16 | 19 | 23 | 27 | 32 |

In 1962, the NIH inaugurated a program to explore the importance of high speed electronic computing and data processing technology in the solution of biological and medical problems. The earliest awards were predominently for the support of general purpose central computer resources, directed at providing service-type computation for all scientists in an academic community. More recently, emphasis on the support of (often peripheral) computing facilities specialized for, and dedicated to, specific classes of problems has been judged to present the more promising opportunity for the investment of limited resources. During FY 1969 the program will be supporting 37 computing centers, engaged either fully or partially in biomedical research.

In addition to providing general computing capability in support of biomedical research throughout the Nation, the existing computer resources have fostered significant technological innovations which presage not only more effective computer applications in the basic medical sciences but also improved delivery of medical care, which - as an accepted matter of national policy - must be extended to all elements of the population. For example, a program has been developed at Washington University, St. Louis, for on-line, real-time mathematical analysis of the electrocardiogram; this new technique should make possible both the design of inexpensive computer-based coronary care equipment and the careful and in-depth study of cardiac arrhythmias. In a markedly different research setting, a large tumor registry file is stored in a computer at UCLA along with a sophisticated repertoire of techniques for the manipulation, retrieval, statistical analysis, and display of the information; this highly interactive system has made it possible for both clinicians and basic scientists to peruse the files, to test hypotheses about tumor incidence, and to identify possible relationships between tumor characteristics and other medical data.

The proposed expansion is responsive to the rapidly increasing recognition of the essentiality of this technology for the solution of many of increasingly complex problems of modern science. While the biomedical research community has been somewhat slow to identify relevant and important applications for computers, the steady progress of the past few years has suddenly opened broad vistas of opportunity. Moreover, prior year investments in manpower training now makes possible a major expansion in the level of program activity. These advances in computer technology and its application not only underscore the need to sustain the vigor of present program concepts but also make clear the desirability of providing additional funds to satisfy the increasing requirements for such technological tools as interactive display-, process control-, and image scanning-systems in order to extend more reliable and comprehensive health research programs and to support health service applications.

This program is managed by the Special Research Resources Branch of the Division of Research Facilities and Resources, and funds for it are included in the General Research and Services Appropriation.

DIVISION OF RESEARCH FACILITIES AND RESOURCES
NATIONAL AND REGIONAL PRIMATE PROGRAMS
(Dollars in thousands)

| | F.Y. 1967 | F.Y. 1968 | F.Y. 1969 | F.Y. 1970 | F.Y. 1971 | F.Y. 1972 | F.Y. 1973 | F.Y. 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants..... | $9,000 | $10,500 | $10,500 | $12,100 | $13,900 | $15,600 | $17,000 | $18,200 |
| Direct operations: | | | | | | | | |
| Inhouse..... | 102 | 106 | 168 | 205 | 240 | 255 | 271 | 287 |
| Contracts..... | -- | -- | -- | 500 | 1,200 | 1,800 | 2,200 | 2,900 |
| Total..... | 9,102 | 10,606 | 10,668 | 12,805 | 15,340 | 17,655 | 19,471 | 21,387 |
| Positions..... | 7 | 7 | 11 | 13 | 15 | 16 | 17 | 18 |

Since its inauguration in 1962, the National and Regional Primate Research Centers program has organized, constructed and initiated operation in seven centers. In the aggregate, these units are functioning at about 60% of planned initial capacity. The original program concept emphasized meeting the needs for suitable facilities and resources for conducting biomedical research on non-human primates and for establishing methods and facilities for breeding and maintaining healthy animals over a long period of time. Evolution of the centers has been away from resources of a general and undifferentiated character, and toward research centers focused on special biomedical problems, a shift in program emphasis found unavoidable if a high calibre staff was to be recruited and retained. The proposed expansion of the established program will simply bring the level of research activities up to that required to use the existing facilities.

A modification of the initial program plan, however, appears necessary since the existing centers probably cannot meet all of the national needs for primates for research. A new program element, essentially a proposal for the large-scale production of non-human primates, is proposed to meet the burgeoning requirements for such animals for studies in the biology of reproduction, in the behavioral sciences, in mental retardation and in a host of other areas of high biomedical scientific opportunity.

For the basic program, supplemental funds are being requested to add 100 additional scientists by 1974 in order to achieve the full research capability of these centers. These funds will be used to provide the necessary supporting staff, equipment and experimental animals to carry out the research investigations. The scientific investigations presently being conducted will be expanded and new areas of research will be initiated. It is anticipated that research employing primates in the areas of tissue and organ transplantation, reproductive biology, behavioral sciences and mental health will increase drastically in the near future.

Studies now being conducted and/or anticipated will require large numbers of primates bred and raised under standardized conditions and with known medical histories. It is becoming increasingly difficult to obtain many of the required species from their natural habitat; therefore, it will be necessary that breeding facilities be established and maintained. Feasibility studies are necessary for the purpose of establishing physiological norms, dollar costs of production and production statistics; these should instill confidence in entrepreneurs and encourage future commercial production. Preliminary information presently being developed at the National Center for Primate Biology and other institutions is considered to be at a stage at which pilot scale ventures are feasible.

This program is managed by the Animal Resources Branch of the Division of Research Facilities and Resources and funds are provided in the General Research and Services Appropriation.

DIVISION OF RESEARCH FACILITIES AND RESOURCES
GENERAL CLINICAL RESEARCH CENTERS PROGRAM
(Dollars in thousands)

| | F.Y. 1967 | F.Y. 1968 | F.Y. 1969 | F.Y. 1970 | F.Y. 1971 | F.Y. 1972 | F.Y. 1973 | F.Y. 1974 |
|---|---|---|---|---|---|---|---|---|
| Research grants..... | $28,463 | $30,443 | $35,677 | $49,300 | $61,000 | $77,000 | $86,900 | $97,700 |
| Direct operations: | | | | | | | | |
| Inhouse..... | 203 | 213 | 229 | 300 | 367 | 415 | 447 | 478 |
| Total..... | 28,666 | 30,656 | 35,906 | 49,600 | 61,367 | 77,415 | 87,347 | 98,178 |
| Positions..... | 14 | 14 | 15 | 19 | 23 | 26 | 28 | 30 |

The General Clinical Research Center program is the major bridge between basic research in the biological and medical sciences on the one hand and application in the human patient on the other. Inaugurated in 1960, the program now supports 91 inpatient centers. The proposed expansion will establish inpatient centers in those new and existing medical schools which presently lack such facilities, and will enable the NIH to establish a new parallel series of facilities for the careful study of disease in the ambulatory patient.

Each inpatient center provides the extensive facilities and specialized personnel necessary to conduct precise studies at the bedside. Since its inception, the program has become the major vehicle for institutional support of clinical investigation. Access to these centers has enabled investigators from a variety of disciplines to translate new knowledge into early clinical application. The pathophysiology of many previously obscure diseases is now well defined and, in many cases, successful therapeutic regimens have been developed. Current investigations in areas such as lipid metabolism, transplantation immunology and perinatal physiology give great promise. Besides providing opportunities to investigate human disease, these centers have become instrumental in the dissemination of new information through publications and demonstrations and have become an essential resource for many training programs for physicians.

A continuing and expanding need for these centers is anticipated. There are currently 25 established and 15 developing medical schools without centers; several have expressed the need for clinical research facilities in order to provide resources commensurate with their expanded research and training programs and to attract capable faculty. Funds requested would provide for 6 new centers yearly and for funding of the existing programs at the level recommended by Council.

Since the preponderance of human disease occurs in ambulatory patients, the need to study this group is evident. By studying the minimally ill as well as those with chronic debilitating diseases, the continuum of human illnesses will be better understood. It may be anticipated that extended studies of many chronic diseases will lead to improved methods of diagnosis, control and prevention. In response to this need, funds are requested to establish outpatient clinical research centers. These centers are intended to be University resources, to provide adequate physical space, a corps of paramedical personnel, improved record systems and the sophisticated laboratory support needed to facilitate long-term studies of ambulatory patients. Two outpatient centers are projected for FY 69 and an annual increment of 10 centers is projected thereafter.

This program is managed by the General Clinical Research Centers Branch of the Division of Research Facilities and Resources and funds for it are included in the General Research and Services Appropriation.

CONSTRUCTION OF RESEARCH FACILITIES

Mr. LAIRD. Dr. Shannon, in your statement and in answers to questions of the chairman, you made it very clear this budget provides for a 6- to 7-percent increase in research support, but it does drastically cut back on construction. A few years ago, in the discussion which you had with me before this committee, it was pointed out, I thought very forcibly and clearly, that facilities were really running behind manpower, that we were making strides as far as personnel were concerned in the area of research.

We were not necessarily making great strides forward with personnel who are delivering services to people. But in the research area, we were going far ahead of facilities for the actual conduct of research. At that time, the committee wrote in a special provision of the bill for the Cancer Institute we took advantage of a little-used piece of legislation, I think it was section 433(a), because we were in a position where facilities had to receive greater consideration.

This budget provides a small increase from the standpoint of the increased costs and the other problems that we face in financing research activities, but I would like to get the rationale of this budget in continuing to cut back on research facilities.

You have not caught up with facilities; have you?

Dr. SHANNON. No, sir. We have not. But the rationale of the budget is this: price-wage increases, quite apart from any increase in sophistication, come to about 4 to 5 percent a year. So that in order to maintain the scientists now at work, the grants item must increase by about that much.

In addition to that, as result of training programs, we have young scientists entering the field each year for the first time. We must find some opportunity for them to express themselves or the money we have expended in their training is in some measure lost. So this budget reflects the view that we must go as far as we can to maintain our research operation. Even though there are serious deficiencies in construction, the impact of our attempt to remedy them through new construction would, in any case, require 3 to 4 years.

Mr. FLOOD. Construction where?

Dr. SHANNON. At the universities.

Mr. LAIRD. These research grants are being increased again in this budget, but 4 years ago the statement was made right here that there was no sense in going ahead and increasing research grants because you had no place to carry on the additional research.

Mr. FLOOD. I wanted to be sure we were not talking about the NIH campus.

Dr. SHANNON. This budget will not provide for an increase in the scientific work force. It will maintain what we have now, the scientific work force in being. So we had a choice of cutting that back in order to allow minimal construction to go forward or maintain the scientific work force in being and then defer the impact of curtailing construction for a 3- or 4-year period.

This will not harm the program so terribly if this curtailment of construction is for a short period. On the other hand, if this were to continue for 4 or 5 years, it would have an extraordinarily serious impact.

For the same reason we held training at about the same dollar level, which means there is not a substantial cutback in training, only a small one. Again, we can let that idle at this time because the impact of the training programs on the performance of research has a delay time of 2 or 3 years. So we are viewing the budget this year as being essentially an emergency budget. We have adjusted it so as to have the least impact on research operation today and during the coming year, hoping that we can retrieve some of the losses during the next 2 or 3 years.

Mr. FLOOD. Outside of bricks and mortar, do you have any bottleneck in research hardware, equipment you use in the laboratory? Is there a bottleneck? The Defense Subcommittee discovered such a bottleneck in oceanography. Do you have any trouble with that?

Dr. SHANNON. Not in that sense; no, sir. The budget will restrict purchasing power of new operations and for new equipment but not to the point where it will be serious long-term damage to the program. The aim of this budget is to attempt to keep the present work force in being and to defer the consequences of the financial restraints to the future.

ANIMAL CARE ACT

Mr. LAIRD. Dr. Shannon, last year the Congress, by almost a unanimous vote, passed a new Animal Care Act. This Animal Care Act, according to some of the medical school people I have talked to requires a substantial expenditure on the part of the schools and other research institutions all over the United States.

I wonder sometimes whether the Congress realized they were including this requirement for a very substantial investment.

What is this construction curtailment going to do to these schools and research institutions that must carry out the mandate of almost the unanimous act of the Congress?

Dr. SHANNON. Mr. Laird, we made this explicitly clear to the committees that heard those bills. On the floor of the Senate, I recall, the question was raised by Senator Pastore and a number of others joined in. They expressed the hope that research facilities construction funds would be provided—preferably on a more favorable matching basis than our 50–50 matching formula—for the renovation and new construction that this legislation requires. But, unfortunately, in the next budget round research facility construction, instead of being expanded, was drastically curtailed and, as you see, in this budget it is curtailed even further.

Mr. LAIRD. It seems to me the Congress, before it acts on a bill like this, ought to realize what it is requiring these schools to do. I know this animal care legislation was very popular legislation. I voted for it, I think everyone on this committee voted for it. But now it has to be enforced this year and next year.

What is the price tag on that bill?

Dr. SHANNON. The price tag on the present legislation is not too bad because it primarily involves holding facilities and commercial enterprises for the care and transportation of animals.

COST OF PROPOSED ANIMAL CARE BILL

Mr. LAIRD. We have a new bill they are having hearings on now that is quite broad. It has been recommended by the administration, and it

has a favorable report from all of the agencies. What is the price tag on that bill?

Dr. SHANNON. As a result of an assessment of the adequacy of animal facilities done 3 years ago—and the situation has not changed now—the general judgment was that 50 percent of the animal facilities used by investigators were adequate, about 25 percent could be made adequate with substantial renovation, and about 25 percent would have to be totally replaced.

The new legislation, with the amendments introduced by Senator Magnuson and Senator Monroney in the Senate, goes beyond last year's. It would apply to the care of animals through the entire investigative process and involves animal facilities for all investigative areas. This would be very costly.

I would point out that the money in this budget, and the carryover from last year, which total about $20 million, cannot all be devoted to replacement of animal facilities even on a 50–50 matching basis. Some of those funds must go to the development of new medical schools.

Mr. LAIRD. I would hope so. We have to take care of human beings, too.

Dr. SHANNON. The funds that are in the budget now would not even touch the needs. It will not permit compliance on the part of medical schools with the new proposed legislation.

Mr. LAIRD. Can you give me a price tag on what it is going to cost? Say we replace 25 percent of the animal care facilities, what is the price tag on that?

Dr. SHANNON. I can supply that for the record. We calculated that at the time Senator Magnuson had hearings on the initial Monroney amendments.

(Information follows:)

It is estimated that there are approximately 30 million net square feet of research space in nonprofit institutions in this country. Of this approximately 18 percent is in animal care facilities. Thus the following total costs are calculated based on replacing 25 percent and renovating 25 percent of the existing facilities. It should be noted that these figures do not include the present needs for additional space or the costs at institutions not eligible for NIH grants.

*Estimated existing animal care facilities*

Total, 5.4 million net square feet; 2.7 million net square feet of animal space which is adequate at present time.

| | |
|---|---|
| 1.35 million net square feet of animal space requiring new construction at $80 per net square foot | $108,000,000 |
| 1.35 million new square feet of animal space requiring renovations at $50 per net square foot | 67,500,000 |
| Total | 175,500,000 |

Based on the present 50–50 matching ratio for major construction and renovations the requirement for Federal funds would average approximately $17,500,000 per year over a 5-year period of which $10,800,000 is for the replacement of the existing inadequate animal care facilities and $6,700,000 for renovation.

The total cost estimate for programs identified or suggested in the proposed Rogers-Javits legislation was calculated in 1967. These figures include post-doctoral training grants, fellowships, animal resources and research, contract support for special studies and dissemination of information. The residual amounts are for additional activities necessary to carry out the new activities proposed in the Rogers bill.

The amounts proposed for the technician training item proposed in section 8(a) of the Rogers bill are minimal and would be utilized to supplement ongoing DRFR funded activities in order to provide assistance for the on-the-job training of animal caretakers.

ESTIMATED FUNDING REQUIREMENTS FOR ROGERS-JAVITS BILL

[In thousands of dollars]

| | Fiscal year 1969 | Fiscal year 1970 | Fiscal year 1971 | Fiscal year 1972 | Fiscal year 1973 |
|---|---|---|---|---|---|
| Sec. 8(a): | | | | | |
| Fellowships | 204 | 200 | 300 | 300 | 300 |
| Training grants (postdoctoral DVM) | 326 | 800 | 1,225 | 1,650 | 1,750 |
| Technician training | 500 | 600 | 700 | 750 | 850 |
| Contracts (including development of working designs, selected research and services, environmental technology, establishment of breeding centers for selected biological models, dissemination of information) | 750 | 1,100 | 1,600 | 2,400 | 2,900 |
| Resources and research[1] (15 percent based on program to date; will be utilized for support of research on diseases and maintenance of laboratory animals) | 5,100 | 9,500 | 10,000 | 12,000 | 13,500 |
| New construction and renovations (50 percent) (possible to support from HRF authorized funds, although this is now oversubscribed with unpaid but approved grants in excess of $41,000,000) | 17,500 | 17,500 | 17,500 | 17,500 | 17,500 |
| Sec. 8(b): Cost of certification | 1,000 | 1,200 | 1,400 | 1,600 | 1,800 |
| Technical assistance and dissemination of information: | | | | | |
| Sec. 9: | | | | | |
| Technical assistance | 750 | 750 | 750 | 750 | 750 |
| Dissemination of information (see contracts sec. 8(a)) | 400 | 400 | 400 | 400 | 400 |
| planning grants | | | | | |
| Administrative costs: Salary, travel, administrative costs for additional staff | 210 | 420 | 550 | 550 | 600 |
| Total costs | 26,740 | 32,470 | 34,425 | 37,900 | 40,350 |
| Included in present budget | 5,630 | 6,111 | 8,310 | 10,530 | 13,450 |
| Total net costs | 21,110 | 26,359 | 26,115 | 27,370 | 26,900 |

[1] Resources include: (1) developing and improving institutional animal resources; (2) diagnostic laboratories; (3) definition of biological models; (4) regional animal resources.

Note: Proposed program budget includes all items except: Technician training construction, and renovation, cost of certification, technical assistance and planning grants.

FINANCIAL DIFFICULTIES OF SOME MEDICAL SCHOOLS

Mr. LAIRD. Dr. Shannon, right now we are facing a situation in this country where there are three or four medical schools that are in danger of having to shut their doors.

Dr. SHANNON. Yes, sir.

Mr. FLOOD. And one dental school.

Mr. LAIRD. They cannot continue under current cost figures. I refer to one school in my own State, Marquette in Milwaukee, and St. Louis University where our old friend, Dr. Felix is now the dean. He used to be Director of the National Institute of Mental Health. We are going forward, talking about building 20 new medical schools and those medical schools will cost—I don't want to use too high a figure, but certainly you could make a case for $70 million.

Dr. SHANNON. A conservative figure, yes.

Mr. LAIRD. But we are going forward with this idea of building these new medical schools with substantial Federal contributions, plans are being drawn for architect-engineer work.

What authorization language is there to save a few of the schools that are in existence, those that already have good faculties and hospitals, and facilities, before we move into the construction of the new schools?

I realize we have to construct new schools because we have a shortage not only of doctors, but nurses and medical technicians. The manpower studies made in the last 12 months are alarming to anyone who will take the time to read them. We talk about some new legislation that will be sent to the Congress.

And there is a message sent to the Congress with a tremendous price tag on it. I have reviewed that message and I find much of it not new, for instance all of the social security benefits paid under medicaid. They have a lot of figures, but when you read it carefully, you find there is not one dollar for medical education in fiscal year 1969. These schools have to be helped now. What do you have under the broad authorizing language that exists for the National Institutes of Health to save these medical schools before they close their doors?

Dr. SHANNON. We have one piece of authorizing legislation, and the Bureau of Health Manpower has another.

Mr. LAIRD. But the special improvement grant program in the Bureau of Health Manpower cannot save these medical schools.

Dr. SHANNON. No, sir. Under our general research support authority, we now are expending between 10 and 11 percent of an authorized 15 percent of our research grant funds. These schools are still paying substantial amounts of the salaries of senior investigators whose work we support. It would be possible to increase the funds under that authorization which I believe in this budget is at the level of $60 million, by about another $50 million and, with suitable direction we could make that available as stabilizing salary supplements for individuals engaged in medical education who in addition are concerned with graduate education and the conduct of scientific investigation—which, in effect, is virtually all of the faculty of medical schools.

Mr. LAIRD. Would you have to do it countrywide?

Dr. SHANNON. No, sir.

Mr. LAIRD. You could do it on a selective basis.

Dr. SHANNON. We could do it on a selective basis. How we would do it would depend entirely on the directions we would receive from this committee because we have substantial discretion in how those funds are expended.

Mr. LAIRD. Dr. Shannon, it seems to me there is a real question of priorities here when we get into the area of construction and aid to the medical schools. We have to consider priorities on animal care facilities and the priorities for educational facilities for doctors, nurses, and medical technicians. It would seem to me if we had to make a choice we should make the choice in giving the higher priority to the development of facilities to train individuals that will be caring for people.

What do you think about the priorities in this area?

Dr. SHANNON. I agree completely, Mr. Laird. I would point out, though, it is not only facilities that are needed, but it is programmatic support the medical schools need. I mean a straight subsidy for the education process.

This is the most serious area, even more so than facilities.

Mr. LAIRD. But in order to build new schools, your greatest immediate cost is in facilities; isn't that true?

Dr. SHANNON. This is correct.

Mr. LAIRD. And it is proposed we build some 20 new medical schools; isn't that correct?

Dr. SHANNON. The figure is variously stated depending upon the year. By 1975 our rough estimate is 20 to 25.

BUILDING FOR WORK ON HOT VIRUSES

Mr. LAIRD. Dr. Shannon, in this budget in the construction account you propose a new building for work with the so-called hot viruses. What is the technical basis for this need?

Dr. SHANNON. There are two broad program areas, one in neurology and the other in cancer. It has been found necessary to concentrate viruses and use them in large quantities in order to get over the barrier of species—susceptibility to a virus. It seems quite likely that the causation of some of the cancers, at any rate, are due to viruses. It is certain that some of the devastating and fatal neurological diseases are caused by viruses. We have now imported into this country, for experimental work, a devastating disease of the central nervous system called Kuru, which we have now been able to transfer to chimpanzees. This is a disease that is uniformly fatal to the human.

Mr. FLOOD. What is the name?

Dr. SHANNON. Kuru. It was found in New Guinea.

Mr. LAIRD. What part of the body does that affect?

Dr. SHANNON. The brain, primarily.

This was taken up and studied primarily because it was a disease which had certain characteristics of an infectious disease—but was not, at that time, thought to be due to an infectious agent—in an attempt to find a research approach to such things as multiple sclerosis and amyotropic lateral sclerosis, the so-called debilitating disease. These two have general characterizations that make them appear as though they are infectious diseases.

When one deals with viruses in relation to a disease that is uniformly fatal, one must have a physical facility that protects not only the staff—the scientists and lab workers—but the surrounding community. If a high concentration of these highly fatal viruses were turned loose, they could have a devastating effect on the staff, supporting personnel and community.

It is believed, also, that the only chance to really push forward on some forms of cancer is to provide for high density inoculation in relatively large amounts. These diseases, we predict, will have a long incubation period. If you succeed, it will be 2 or 3 or 4 years before the success is clearly apparent and one does not have the right to expose staff, the supporting personnel, and the surrounding community to this potentially hazardous type of biological agent. One must provide the highest degree of containment of the agent that is possible.

You may remember that this committee provided NIH with funds to set up two small experimental setups to enable the Cancer Institute to explore how it is possible to contain such highly hazardous agents. Since that time the agent for the central nervous system has come along and they are well along with work on that. Initially we felt we could wait for a gradual development of a facility and perhaps satisfy this need 4 or 5 years from now. It now turns out that we have,

essentially, to stop the work on the central nervous system viruses at this time because of inadequate facilities.

It seems likely that in another 4 or 5 years it will require more than a single center. We may well be getting into a situation comparable to that in which the Department of Agriculture found themselves during World War II when they were studying some of the very hot animal viruses. They set up specialized research facilities on off-shore islands in order to contain the diseases. But here we are not dealing with viruses that can only be transmitted from animal to animal but perhaps from animal to man so that the hazard is even greater. Until resources of the type that were proposed and discussed previously are available we would not feel free to enter this field. I anticipate that in the coming 3, 4 or 5 years it will probably be necessary to set up two or three more such centers. But the need is here today and the study cannot go forward until that need is satisfied.

### Ninth Report of Committee on Government Operations

Mr. Laird. During the past 15 years I have taken particular interest in the activities of NIH and have closely followed the development of its programs. I am firmly convinced that there are few Federal activities as important as a practical concern for improving the health of the American people. I am equally convinced that this can only be achieved through a vigorous national research effort for which the Federal Government must supply a major share of the support. I have been much impressed by the intelligence, initiative, vigor, and dedication with which those responsible for the NIH programs have attacked the task of building up a national medical-research capability that is now second to none. I am proud of the fact that the committee on which I serve has played a significant part in making this possible.

I am therefore disturbed that another committee of the Congress has issued a report which questions the way in which these programs have been—and, more particularly, are being—administered. The ninth report by the Committee on Government Operations, issued last October, is mainly concerned with some specific management problems and with some policy decisions with which the Committee on Government Operations disagrees. However, the conclusions drawn from these issues in the report and the tone of the report are used to cast doubt on the effectiveness of the NIH programs. This is a serious implication which I would like to explore. Can you make a factual assessment of the overall effectiveness of NIH activities in terms of the extent to which they are accomplishing their purpose?

Dr. Shannon. The sole purpose of the NIH programs is to enhance man's ability to deal with disease and, thus, to advance the health of the American people. NIH is by far the largest single source of support for medical research in this country—about 40 percent of our total national expenditure for medical research is now provided through the NIH appropriations. NIH therefore plays a substantial role in determining the character and directions of our national medical research effort. It is not merely fortuitous that the most dramatic period of medical progress coincides with the period of NIH's rapid growth.

There is in progress a revolution in the practice of medicine as the result of research. The American Medical Association has reported that the introduction of new drugs and other therapeutic products has been so dynamic that seven out of 10 now on the market were not available 10 years ago. New knowledge has greatly changed both the approach to the treatment of disease and the attitude of the practicing physician to science. In fact, the impact of science on the capability to diagnose and treat disease has become so great that physicians, who were formerly mainly concerned with the application of existing empirical knowledge which changed very little from year to year, now require broad programs of continuing education if they are to avoid a very high rate of technological obsolescence. NIH can fairly claim to have made a major contribution—and, probably, the major contribution—to this dramatic change.

Last year, the AMA's Commission on Research, after 3 years of investigation, said in its report that—

> The public has benefited immensely from the total effort in medical research which largely has been carried out since World War II under the aegis of the National Institutes of Health.

And that—

> The improved quality of patient care currently available reflects, to a significant degree, the expanded research knowledge created in the last decade.

THE QUALITY OF RESEARCH SUPPORTED

Mr. LAIRD. The most serious criticism in the report is the charge that the quality of research being supported by NIH has declined to the point where "a much lower level of competence has replaced high quality as the standard for determining what research is worthy of Federal support." This is contrary to everything that this committee has learned about NIH programs. Witnesses appearing before this committee in the public sessions have been almost unanimous in emphasizing the high standards of quality of the NIH programs. In fact, the criticism which this committee has encountered has been just the opposite; that NIH quality standards are so high that many investigators and institutions are unable to qualify for support. It is important that the facts of this matter be made clear.

Has NIH lowered is quality standards?

Dr. SHANNON. Most certainly not. NIH research support—now as in the past—is provided only for a research proposal judged by the applicant's peers in his field of science to be a worthwhile project with a high probability of yielding useful results and which is judged by an NIH Advisory Council to have significant relevance to the program objectives of NIH.

Mr. LAIRD. The report states that "it is unclear whether the NIH objective is to support only high quality research or to extend support to all competent investigators." What is the NIH objective?

Dr. SHANNON. There is no basis on which one can draw a valid a priori distinction between the competence of an investigator and the quality of his research—as the Fountain Committee seems to suggest.

The objective of NIH is to support competent research projects judged likely to contribute to the solution of disease problems. The work that must be done to resolve these problems covers a broad spec-

trum of activities that ranges from highly imaginative and technically sophisticated studies, such as reasearch on genetic mechanisms, to equally important but less colorful tasks involving well-established techniques, such as many biometric and epidemiological studies and much painstaking laboratory research. It would be disastrous for the progress of medicine if support were limited to exciting and dramatic projects. Occasionally some major breakthrough—like the discovery of the effect of penicillin, which, incidentally, was unplanned and accidental—will greatly advance the state of the art, but the bulk of medical progress is due to careful, undramatic work that expands the solid base of existing knowledge. It is understandable that a lay observer would not regard some of this work as high quality research. Yet it is as important to the development of the structure of scientific knowledge as the work of a structural engineer is to an architect.

The Fountain Committee report says: "If pedestrian research contributes importantly to the advancement of science, that fact has not been brought to our attention." The term "pedestrian research" has a highly derogatory connotation but no real meaning. If what is meant is "lacking brilliance," the Committee must understand that the vast body of scientific knowledge has not been built—and cannot be built—by a series of brilliant forays. The brilliant achievements—the so-called breakthroughs—are all too frequently only recognizable long after the event and usually only in the light of the less colorful work, by many hands, which they made possible. Moreover, these brilliant achievements are themselves the culmination of much dogged research by many others. In fact, the more immediate contributions of research to the improvement of diagnosis, treatment, and prevention are more likely to come from the work of the merely competent investigators than from a few brilliant achievements which usually require years of painstaking elaboration by other investigators before they can be applied.

The criteria by which grant applications are judged have been clearly stated. They are—

The general scientific significance and relevance to PHS-related research of the proposed study and its objectives;

The technical adequacy of the experimental design or the research approach;

The competence of the proposed investigator or group to pursue the project;

The adequacy of the available resources and of the scientific and administrative environment;

The necessity of budget components requested in the application in relation to the proposed research and to resources described as currently available; and

The appropriateness of the period of support requested.

The quality level of an application is assessed against these criteria. Two judgements are made. The first is whether the proposed work warrants support. The second is a comparative judgement on the probable value of the work in the light of the current state of the art in its field. This is not—and there cannot be—an absolute and abstract determination of quality against some fixed and generally applicable standard.

Mr. LAIRD. The Fountain Committee report states that the quality of a project is denoted by its priority rating assigned by the scientific review panels. On the basis of these ratings, it charges that the quality of NIH-supported research is declining. Do these data really mean that there has been such a decline?

Dr. SHANNON. No; they do not. The use made of the priority ratings in the report is misleading. The report ignores the fact that priority scores are assigned only to research projects judged worthy of public support. The standards of this process are rigorous. Almost half of all new research grant applications are rejected, during the initial review process, as not worthy of Federal support. All of the applications to which priority ratings are assigned have thus already been judged to have scientific merit.

The purpose of the priority score is not to quantify quality, in an absolute sense, but to provide a means of selecting, from a large number of worthy proposals, those that should have priority for support from the limited funds available. The priority score does, to some extent, reflect the quality of the proposed project but also its relevance and its urgency and a judgment by the reviewers of where research emphasis is needed. For example, a sound proposal for a research project on a relatively neglected problem will usually receive a higher priority score than a proposal of equal quality in a field already under fairly intensive investigation. The priority score thus reflects scientific choice as well as scientific merit.

Contrary to the impression conveyed by the report, there has been relatively little change during the past 8 years in the distribution pattern of the priority scores of research grant applications recommended for approval. In fact, during the past 2 years there has been a slight increase in the proportion of applications falling in the highest priority group but no significance is attached to this change.

Mr. LAIRD. What has been the opinion of other groups that have examined the NIH research programs about the quality of the research being supported?

Dr. SHANNON. The Wooldridge committee, after an exhaustive scrutiny of NIH research administration in 1965, came to the conclusion that:

> Despite the tenfold increase in NIH support of research during the last 8 years, there is no evidence of overall degradation in quality of the work supported. On the contrary, there is good evidence that the average quality is steadily improving. This appears to be a consequence of a rate of increase in the production of competent biological research scientists matching the overall rate of increase in research support.

The American Medical Association's Commission on Medical Research, after its review of NIH activities, concluded that:

> The study section arrangement organized by the NIH for review of proposed project grants through panels of outside academic experts (or peer groups) has been successful in identifying and supporting research of quality.

### NEW PROGRAM DEVELOPMENT

Mr. LAIRD. The report is critical of NIH's procedure in the development of new programs. In this connection, the report criticizes the manner in which the new health sciences advancement awards program

was launched and questions the propriety of making a single large grant to the Sloan-Kettering Institute.

The report questions the statutory authority for the health sciences advancement awards. What is the position?

Dr. SHANNON. The legality of this program was clearly confirmed well before the Fountain committee report was issued in October. You will recall that the question of statutory authority for this program was raised during last year's appropriation hearings. In fact, last May the House Committee on Appropriations, in its report on the Labor-HEW bill directed that no further grants be made under the health sciences advancement awards program until the Comptroller General had ruled that there was legislative authority for it. In compliance with this direction, a ruling by the Comptroller General was requested by DHEW. On June 30, 1967, the Comptroller General ruled that the statutory provision under which the HSAA program was initiated was adequate for the action taken.

Mr. LAIRD. I understand from your testimony at these hearings that the procedure for selecting the recipients of the first few health sciences advancement awards was an experimental approach or in the nature of a feasible study. Are you yet in a position to say whether this program is feasible and justified and, if so, what procedure will be adopted for making future awards?

Dr. SHANNON. Two years' experience with this program has clearly demonstrated both its feasibility and the national need for such a program.

The basic aim of the HSAA program is to increase the number of generally excellent institutions engaged in health-related research and the attendant training of scientific manpower. The two original HSAA awardees have made significant progress in this direction. In one, the research in the medical sciences, which was fragmented and diffuse, has been greatly strengthened by the consolidation of ongoing research and the recruitment of outstanding scientific leaders for key positions. The second awardee has assembled distinguished leadership for four of its preclinical departments and there has already been a notable rise in the quality of its graduate students.

This program was discussed freely with a number of academic groups and, while it was judged not advisable to seek broad participation during the initial year, the belief that NIH moved in a secret manner, as has been suggested, is erroneous.

Interest on the part of academic institutions in this program is extremely high. Nearly 140 institutions have already applied for assistance under the program. On the basis of the effects achieved in the first two grantee institutions and the evident opportunities demonstrated in the applications examined to date, NIH is convinced that expansion of the program is justified at as rapid a rate as available funds will permit.

As a result of experience with the preliminary review of a limited number of applications, the process of evaluating university proposals has now been established on a solid base. In general, it now conforms to the dual peer review system in use at NIH. Applications are reviewed by staff, by a recently constituted HSAA advisory and review committee, and by the National Advisory Health Council. The HSAA

advisory and review committee is composed of 16 members, chosen to include university administrators and research scientists. Awards will only be made on recommendation by the National Advisory Health Council. All interested institutions will be considered equally eligible for each cycle of competition. It should be added that the early development of this program involved considerable discussion with institutions and consultants before its actual initiation.

Mr. LAIRD. The Fountain committee does not challenge the legality of the Sloan-Kettering grant, but takes the view that "the Surgeon General acted unwisely in using the broad discretion" given him by section 301(i) of the Public Health Service Act which permits him to adopt "such additional means as he deems necessary or appropriate" for the conduct and support of research. The wisdom of using this authority in a particular case is a matter of opinion rather than of law.

Why was it "necessary or appropriate" to make a single large grant to the Sloan-Kettering Institute?

Dr. SHANNON. The principal reason for making a single, comprehensive grant to SKI was to facilitate a comprehensive research attack on cancer. Cancer is a diverse array of diseases whose basic causes are unknown and the biological processes involved are extraordinarily complicated. Many aspects of cancer research therefore require a concerted approach involving many scientific skills. For this reason, the National Cancer Institute has sought to stimulate and support the development of research institutions—or centers within institutions—wholly devoted to cancer research. SKI is such an institution and it has, for a number of years, drawn about half of its financial support from the National Cancer Institute. However, this support has been in the form of individual project grants which, in the case of a specialized institution such as SKI, represents a piecemeal approach to what should be cohesive activity—and for which a single support device is more appropriate.

The program of an institution wholly devoted to research on a specific disease, such as cancer, is also more appropriately reviewed by assessing the program as a whole—and from the point of view of relevance to the disease. However, the initial review groups at NIH (that is, the study sections) are organized along disciplinary, rather than disease, lines. Each study section reviews individual project applications primarily from the point of view of scientific excellence and their relevance to the scientific discipline or specialty with which the study section is concerned. The study sections are thus not in a position to take a panoramic view or to make a comprehensive judgment about the total program of an institution that is wholly devoted to research on a specific disease but which involves a broad spectrum of scientific disciplines and medical specialties. In these circumstances, a single grant, covering the whole of the support to be provided by NIH, serves the public interest by providing a coherent review and assessment of all the relevant work.

From the institution's point of view, it is also a more appropriate support device. It permits the institution to make a clearer and more informative presentation of its research program for review and evaluation by NIH. At the same time, it greatly simplifies the administration both for the institution and for NIH. The single grant gives the institution a firmer base for planning its future activities and greater

flexibility in addressing itself to new research needs as they arise. The assurance of support for a major segment of its program also facilitates the recruiting and retention of highly qualified investigators. Finally, dependence on a single grant for the Federal share of the institution's support will obviously stimulate more rigorous management of the Federal funds because so much is at stake. The maintenance of the high quality of work and its continued relevance to the solution of grave problems in the cancer field is monitored by the participation of the senior staff of the National Cancer Institute in the annual program review of the Sloanse-Kittering Institute.

The amount of the single grant made to SKI was slightly less than the total of the then existing project grants which the single grant replaced.

Mr. LAIRD. Does NIH intend to make any more of such grants in future?

Dr. SHANNON. NIH has no specific plans for making other single-grant arrangements. However, there are a number of other situations in which such a grant may well be more appropriate, effective, and efficient than present methods of providing support. If the arrangement with SKI proves to be as satisfactory as expected, consideration will be given to making further use of this device in similar circumstances. The criteria will be that the grantee institution—

Is devoted largely, if not exclusively, to a categorical research objective;

Has a comprehensive research program in its field;

Is basically a noninstructional institution with a concentration on research not usually possible in a discipline-oriented department university;

Has a science program that is well established and of recognized excellence; and

That the institution has demonstrated that it has effective scientific and administrative management.

Mr. LAIRD. Are the present administrative procedures at NIH adequate for the fair and efficient development of new programs? Or what changes do you recommend?

Dr. SHANNON. As I already indicated, I am convinced that the NIH procedures are adequate—not because they have reached a stage of perfection but because they are not static. No set of procedures and no administrative machinery will be equally well suited to all programs or for all time. As programs change or new ones are developed, administrative procedures must change or new ones must be developed. The NIH administrative machinery has the flexibility, the awareness of the need for change, and the ready access to competent advice to insure that procedures can and will be adapted to new program needs.

The process will occasionally involve some growing pains and initial decisions will not always be the right ones. But the system for making these decisions is flexible and responsive. The initial decisions, therefore, do not become permanent procedures until we are satisfied that they work. There are many examples of this evolutionary process in the long history of NIH program development. The experimental approaches used in launching the Health Sciences Advancement Awards and in making a single grant to Sloan-Kettering are the latest examples of this process.

ADEQUACY OF MANAGEMENT DEVICES

Mr. LAIRD. The third general area of criticism in the Fountain committee report concerns the adequacy of NIH management of existing programs. Most of this criticism is directed at various aspects of the administration of grants but some of it is 5 years old, having been made on the basis of the committee's investigations in 1961 and 1962. Although the report states that NIH "has made relatively little effort to improve its administration of grants" during the past 5 or 6 years, it was my impression, from the testimony at the appropriation hearings during these years, that a number of important administrative changes had been made.

Have any significant steps been taking during this period to strengthen the management of the grant programs?

Dr. SHANNON. Yes, a great deal has been done. The entire process of grant management—from the Institutes and divisions to the Office of the Secretary—has been extensively overhauled and strengthened.

A new Division of Grant Administration Policy, under the general direction of the Comptroller, has been established at the department level.

The Department has taken over the function of external grant audit as well as the determination of indirect cost rates.

A new system of grant payment has been developed to reduce the cash outflow rate to the level of current requirements.

Additional personnel has been assigned to program and grant administration and a special training program has been instituted for this staff.

The handling of grant data, including review and approval data, has been improved and expanded by the use of computer processing.

Revised grant-management policies and procedures have been published in manuals (for use both at NIH and by the grantees) and clarified regulations governing the exercise of basic grant authorities have been published.

An extensive pilot study is now in its fourth year under which the managerial responsibilities of grantee institutions have been enlarged with a view to strengthening their role in the management of grant funds.

To assist in the further development of sound grant policies and improved grant administration in grantee institutions, the Secretary recently established a Grant Administration Advisory Committee consisting of representatives from all sections of the grantee community. This committee will give grantees a greater awareness of the conditions governing the use of public funds and will give Federal administrators a better insight into the problems and needs of institutional management.

There has, indeed, been substantial change and improvement in grant administration during the 6 years since the Fountain committee reviewed these matters in 1961 and 1962. A number of the current recommendations of the committee had been incorporated in NIH procedure prior to the issuance of its 1967 report.

Mr. LAIRD. This committee has repeatedly given intensive consideration to the problem of indirect cost payments. In 1965 the commit-

tee took the initiative in eliminating the arbitrary 20 percent ceiling on indirect cost payments and replacing it by a simple requirement that the grantee institution make some contribution to the total cost (including indirect costs) of a grant project. On the floor of the House, the late chairman, Mr. Fogarty, explained that this meant that the "grantees would be participating to the extent of perhaps an average of 5 percent." How has the change in the legislation affected the indirect cost problem?

Dr. SHANNON. The effect of this provision has been, as intended, to permit the Federal Government to reimburse an institution for all but a small part of the full cost of grant-supported research. However, a grantee institution's actual indirect-cost rate must still be determined to make it possible to compute its entitlement to reimbursement for indirect costs. The determination of this entitlement continues to present policy and operating problems. Available indirect-cost rates have not been computed on a uniform basis, they are not equally applicable to varying types of research, they are constantly changing due to increasing costs and changes in the administrative arrangements at grantee institutions, and there are complex questions about their applicability to off-campus research. These problems are under active study with a view to the further improvement in the administration of indirect costs and to extend the use of the fixed-predetermined rate method of paying indirect costs authorized by Public Law 87-638. Responsibility for determining indirect-cost rates was consolidated in the Office of the Assistant Secretary of the Department some 2 years ago.

Mr. LAIRD. What steps have been taken to insure that the present system of payments for indirect costs does not lead to the sort of problems that seem to have resulted from the procedures used before 1965?

Dr. SHANNON. Since December 1965 no indirect-cost payments have been made to institutions that have not submitted an indirect-cost rate proposal. A determined effort is being made by the Office of the Secretary to establish—and maintain—current and reliable indirect-cost rates for all grantee institutions. In connection with the use of the fixed-predetermined rate method of payment arrangements are being made to establish the validity of a prior year's rate as the basis for setting a forward rate.

Mr. LAIRD. The Fountain Committee report quotes the view of "an outside management consulting firm retained to study the Cancer Institute's organization and procedures" in support of its criticism of a lack of central management at NIH. What were the circumstances that led to this study and is it still relevant to the situation today?

Dr. SHANNON. This study was undertaken nearly 7 years ago. It was made at the request of NIH itself under a contract which the National Cancer Institute awarded to McKinsey & Co., Inc., in June 1961. It has long since served its purpose and is no longer relevant to the current scene. The research-grant program of NCI had grown very rapidly between 1956 and 1961 and there had been a considerable increase in staff. It became apparent to administrative officials at NIH—including the new Director of NCI who had been appointed in July 1960—that, in view of these changes, a reorganization of the grant function of NCI was needed. In asking McKinsey & Co. to undertake the study, NIH directed that the framework of the total

NIH extramural operation be considered and that the objectives, concepts, and methods of the overall NIH extramural operation be appraised.

As a result of the McKinsey study, the extramural area of NCI was completely reorganized. This reorganization, in turn, set a pattern that was adapted by other institutes. In subsequent years, NCI has been further reorganized to met changing conditions and new administrative problems. The 1961 findings of this study are thus no longer applicable to the current situation.

Mr. LAIRD. The report again quotes your statement, made during the Fountain Committee's 1962 hearings, that after research projects are selected for support all subsequent administrative actions are essentially trivial.What did you mean by this phrase and do you still hold this view?

Dr. SHANNON. This much quoted phrase is from my opening statement to the Fountain Committee at a hearing in March 1962. At the end of a lengthy passage, in which I was attempting to explain the fundamental objectives of the NIH research grant programs and the philosophy that underlies their administration, I said:

"Selection of good men and good ideas—and rejection of the inferior—is the key. All subsequent administrative actions having to do with the adjustment of budgets, and so forth, are essentially trivial in relation to this basic selection process."

I realize that the phrase "essentially trivial" was ill-chosen and that I probably overstated the case I was trying to make. At the end of the hearings, Mr. Fountain reread the passage containing this phrase and said:

> You are sold on what you are doing. I think that is fine. But I think you are so sold on it that in your statement you added undue emphasis to one element without taking into account another very important one.

He was, of course, right. I then reiterated my view and concluded by saying:

> I am so concerned with the selection of top scientists—with the development of support under terms and conditions conducive to performance at full capacity—that I think all things short of that must be secondary. This doesn't mean that because they are secondary, they are unimportant.

I do, indeed, still hold this view about the overriding importance of the selection of good men and good ideas—as, I think, any responsible administrator of NIH must. There was, of course, nothing in my 1962 statement to suggest that NIH was unconcerned about the effective expenditure of grant funds. It is a pity that the phrase, which Mr. Fountain recognized as overly emphatic, is now so often quoted out of context.

Mr. LAIRD. Please supply for the record a summary of the Department's response to each of the 17 specific recommendations made in the report and the Secretary's letter of transmittal.

Dr. SHANNON. I shall be glad to.

Mr. LAIRD. I have no further questions.

[The material requested follows:]

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON

February 26, 1968

Dear Mr. Chairman:

I am pleased to transmit to you the enclosed document which contains the comment of this Department on the Ninth Report of the Committee on Government Operations entitled "The Administration of Research Grants in the Public Health Service". The findings and recommendations of the report have been studied carefully within the Public Health Service and by the staff of the Office of the Secretary. The views expressed in the enclosed comment and the positions taken on the recommendations are the consequence of these reviews and have my full approval.

This response is based on a thorough review of the policies, procedures, and organization for the management of research grants within the Department. While effort to obtain progressive improvement in these arrangements remains a continuing responsibility, I am convinced on the basis of this review that the structure and approach of the departmental grant-management processes are basically sound and capable of effective discharge of the responsibilities involved.

The magnitude of NIH programs, which are the principal object of your committee's examination, is now of the order of $1.2 billion. This reflects the current managerial dimension of this activity. The twelvefold increase in these expenditures since 1956 is a gauge of the rate of growth and the consequent complexity of the task of program and policy development.

A national program of this importance, undergoing rapid change in an area requiring extensive policy and procedural innovation, must, in the public interest, be subject to continuing scrutiny and evaluation. The National Institutes of Health has been subjected to numerous such inquiries. Among these studies, those conducted by your committee have, without question, contributed to the improvement of procedures and the evolution of public policy in the conduct of these grant programs.

There is much in the report recommendations with which this Department concurs and little where there is any difference in principle. Thus, of the seventeen major recommendations in the report, we have no disagreement in substance with fourteen. Only in three of the recommendations is the Department not in accord with the committee's view. The enclosed report develops the reasoning and conclusions with respect to these three recommendations.

Of the fourteen recommendations where there is agreement in principle, action is already under way, or has been accomplished, in four; in an additional eight, while there is general concurrence, the Department approach may differ somewhat from that recommended by the committee, and specific plans to determine a final course of action are under study or in the process of development. In the remaining two of these recommendations, while the Department concurs, the principal action lies within the Executive Office of the President and we are making this report available to the Bureau of the Budget for their consideration.

Beyond specific actions taken and planned in the areas examined by the committee, a series of broad changes in the Department have been taken which will contribute substantially to the purposes of the committee report:

. . . The establishment of the Office of the Assistant Secretary, Comptroller, has provided the means to substantially strengthen the financial management capabilities of the Department and bring to the management of departmental grant programs a coordinated rational approach which will obviate many of the difficulties of the past.

. . . The development of a Departmental Planning, Programming and Budgeting System under the Assistant Secretary for Program Planning and Evaluation now permits the critical examination of new and expanded program plans in the context of emerging needs, national policies, and the conditions of responsible administration.

As a final point, I believe it important to emphasize, as the enclosed response does, that the postwar growth of medical research in the United States is surely one of the great contributions of this Nation in advancing human well-being. The role of Federal programs and particularly those of the National Institutes of Health, in providing impetus and support for this remarkable scientific effort, has been broadly acknowledged. To have participated in the further planning and development of these activities over the past two and one-half years has been, for me, both a great challenge and a special satisfaction.

I should like to assure the committee of my firm confidence in the leadership being provided these programs through the Surgeon General of the Public Health Service and the Director of the National Institutes of Health. We are fortunate, indeed, to have such able and dedicated men in the public service. In order to maximize their effectiveness, we are endeavoring to improve the present organizational arrangements. The reorganization of the health functions of the Department now under consideration has as its principal objective the effective assertion of national leadership, policy development, and program coordination in health matters to further overall progress in improving the national health.

I am taking the liberty of transmitting copies of this response to Senators Hill and Hayden, and Representatives Mahon, Flood, and Staggers in recognition of their interests in this matter and their committee responsibilities.

We shall be pleased to provide the committee with further information on this matter or respond to additional requests as you may desire.

Sincerely,

/s/

Secretary

Honorable L. H. Fountain
Chairman, Inter-Governmental
Relations Subcommittee
Committee on Government Operations
House of Representatives
Washington, D. C. 20510

Enclosure

Departmental Position on the Recommendations
of the House Committee on Government Operations

Indirect Costs Overpayments

"Recommendation No. 1.--The Committee strongly recommends that the Surgeon General make suitable arrangements to assure the uniform application of the Department's indirect cost rate information by all granting units of the Public Health Service. With respect to the use of off-campus rates, which are normally lower than on-campus rates, the Committee recommends that the Public Health Service obtain sufficient information in grant applications and in subsequent reports to identify the locations at which the research is performed."

In respect to Recommendation No. 1 of the Committee's report, the arrangements proposed therein have already been accomplished. A system to assure the availability of indirect-costs information and uniform policies in its application throughout DHEW has been established. Provision has been made for securing additional information on the location of research activities, to assist in ascertaining the application of differential off-campus indirect-cost rates.

Despite the progress in this area, the handling of indirect costs continues to present policy and operating problems which are now under study to permit further improvement:

1. Because of the varying sources and currency of indirect-cost rates, and the varying character of research projects, available rates may not be directly and simply applicable, presenting continuing problems to program administrators involved in determining the amounts of awards.

2. Increasing costs and the changing administrative arrangements in institutions limit the durability of a given rate and the extent to which use can be made of the fixed-predetermined rate method of paying indirect costs authorized by P.L. 87-638. This forces continuation of the process of making provisional allowances for indirect costs, with the consequent burden of recalculations and adjustment. The Department is endeavoring to extend use of the fixed, predetermined rate method in administering indirect-cost activities.

3. The determination of the appropriate circumstances for the use of "off-campus" indirect-cost rates can be extraordinarily complex. Various factors enter into whether an off-site rate should be used. A specific study is now under way aimed at developing criteria for establishing off-site rates and the mechanics for identifying the circumstances where such rates should be applied.

Improving Indirect-Cost Determination

"Recommendation No. 2.--The Committee endorses the concept of assigning Government-wide responsibility for establishing indirect cost rates with all institutions of a given type to a single Federal agency, with each type of institution audited by one Federal agency only. The Committee recommends that this concept be vigorously pursued by the Bureau of the Budget and other interested agencies so that a final Government-wide plan covering all institutions will expeditiously be established."

While deferring to the primary responsibility of the Bureau of the Budget in respect to Recommendation No. 2, it should be noted that the Department has long advocated this objective and sought to engender its exploration. Thus DHEW is in full accord with this recommendation.

General Research Support Grants

"Recommendation No. 3.--To eliminate some of the abuses that have developed in the general research support program, the Committee recommends that program policies be changed immediately to:

(1) Determine each GRS grant on the basis of the recipient institution's research expenditures from Federal sources alone. The Committee does not believe the premium given for non-Federal research funds under the existing formula operates as a meaningful incentive for institutions to seek private funds. Rather, this premium favors research organizations over institutions of higher education, and has been difficult to administer and wasteful of Federal research money, and

(2) Exclude from the computation base for a GRS grant all Federal payments for research which include fees above actual research costs.

Additional recommendations concerning the GFS program appear below."

In respect to Part I of Recommendation No. 3 of the Committee report, the Department has directed PHS and NIH to submit to the Secretary a plan for modification of the formula utilized for calculating the awards under the General Research Support Grant program which provides for the elimination of the premium factor for nonfederal research expenditures, as well as other changes considered desirable, to be effective with the GRS awards made for fiscal year 1969. This plan would encompass such interim arrangements as may be necessary to moderate abrupt changes in the magnitude of grants now being received by institutions whose entitlement may be substantially affected by the revised formula.

In respect to Part 2 of Recommendation No. 3, instructions have been given to PHS and NIH to require institutions to exclude as entitlement claims for GRS awards all Federal research contract funds which include fees above actual research costs. The amount of specific fees on such contracts are, under present policies, excluded from the entitlement calculation. In view of the Committee's concern of the data furnished in respect to the Stanford Research Institute, PHS and NIH have also been directed to take appropriate action to the extent that applicable policy and practice in respect to contract fees have not been observed.

Health Sciences Advancement Award

"Recommendation No. 4.--The committee strongly recommends that no future grant programs be initiated by NIH or the Public Health Service without fair and open competition after the purpose and the policies of the program have been carefully developed and publicly announced.

"Recommendation No. 5.--The committee further recommends that before any new grant program is started, or a major change is made in the existing program, the proposed regulations for the program be published in the Federal Register so that interested parties may have an opportunity to express their views. The final regulations should be approved by the Secretary before issuance.

"Recommendation No. 6--The committee recommends that before any new program is initiated in the Public Health Service without specific statutory authorization, the program should be formally reviewed by the Department and the Executive Office of the President to determine its conformance with national education and science policies. Also, a written opinion concerning the legality of any such program should be obtained in advance from the HEW General Counsel.

"Recommendation No. 7--The committee further recommends that no additional HSAA awards be made unless and until PHS obtains specific legislative authorization for this program."

As a matter of general practice, vigorous open competition governs awards of the funds appropriated to NIH for research project grants, training grants, fellowships, and facilities construction grants. Programs such as these, once well established, publish statements describing their objectives, eligibility requirements, application formats, and the process for review and approval. When features distinctive enough to require amendment of the PHS regulations emerge, the prescribed formalities, including publication of contemplated changes in the Federal Register, are observed.

Thus, NIH has long respected and prized the tradition of public administration that gives all potentially eligible claimants equal access to appropriated funds. In the administration of NIH Research Grant programs, elaborate machinery has been developed over time for informing potential applicants, for the filing of applications, and for subjecting these to careful review according to clearly understood criteria of scientific merit and program relevance. But it is important to note that this widely known and respected framework emerged only after considerable experimentation and progressive modification based on experience. Throughout this period new program developments were initiated in limited trial forms as a basis for assessing the validity of the concepts involved and the procedural adaptation required. From

such tryouts the basis for broader efforts and information required for adequate public announcement was formulated.

It seemed clear, after careful consideration, that the best interests of the Government and the academic community would be served if a similar approach were exercised in the experimental phases of the HSAA program. Initiation of such an experiment on a small-scale basis appeared to be an approach that would lay the groundwork for a soundly conceived formal program when and if expansion on a national scale could be justified. After first-hand experience had been garnered, program objectives as well as the policies and procedures for attaining them could be defined in terms of greater precision and specificity than those general ones which were the best possible within the existing state of knowledge. The rationale for establishing the eligibility requirements for various classes of institutions would also become more evident.

In the event that the feasibility study did not yield encouraging results, a pilot program launched cautiously, pragmatically, and without extravagant promises could be terminated before large sums of money had been committed. For while large awards to potential "centers of excellence" might turn out to be useful to the grantee and to the Nation in important ways, they would only be justifiable under this program if they produced the "quantum" increase in capability required to establish a true center of excellence in the health sciences.

Thus, the Department is persuaded that the conditions which prevailed at the time justified NIH's exercise of limited experimental option even though the number of institutions involved might have been larger. Beyond undertaking what amounts to pilot efforts under appropriate terms, the Department concurs fully with the general procedure advocated implicitly in the Committee's report: that new formal programs be inaugurated after public announcement and with open competition.

Therefore, the Department's reaction to Recommendation No. 4 is concurrence in general, but with clear recognition that under exceptional circumstances, such as those prevailing at the time the HSAA program was inaugurated, the constituent agencies of DHEW must be permitted the flexibility under appropriate Departmental guidelines to experiment with imaginative and creative program innovations so essential if national needs are to be responsibly served.

The acceptability of Recommendation No. 5--for the publication in the Federal Register of the proposed regulations for new programs and the major changes in regulations for existing ones--depends on the definition of "new" and "existing." The Department would have no objection to supplementing the highly effective public announcement procedures traditionally employed by NIH with use of the Federal Register when it has been determined that new programs (1) have completed their experimental phases, (2) have encountered and solved the major administrative problems that usually appear during early operational phases of novel endeavors, and

(3) have been expanded to a significant scale. Until such time, an agency needs maximum flexibility to be responsive to unexpected situations, and needs freedom from ponderous and formalistic procedures in order to modify policy rapidly in the light of lessons taught by operating experience.

The use of standing and ad hoc advisors and advisory committees, and of National Advisory Councils, has been a very effective mechanism for soliciting the opinions and the reactions of interested parties. In the same context, major changes in existing programs, when important, widely applicable, based on extensive experience, and viewed as relatively permanent, should also be published in the Federal Register. Standard procedure, of course, requires the Secretary to approve and issue such regulations.

Statutory Authority. The concerns of the Committee on this score take two forms: a challenge of the adequacy of existing authority, with the implication that administrative actions taken by NIH in starting the program were illegal; and an insistence upon the need for explicit statutory authorization for the HSAA program.

The legislative history of Public Law 86-798, which authorized grants for general support of the research and research training programs of certain classes of institutions, clearly envisaged the broad exercise of discretion in the design of detailed instruments to carry out the purpose of the law. However, the adequacy of the statutory authority for the program was challenged in the spring of 1967 in the process of examination by the Committee on Appropriations of the U.S. House of Representatives of the President's budget requests for fiscal year 1968. As a result, first the Office of the General Counsel for the Department of HEW and then the Comptroller General of the United States were requested to rule on the question of adequacy of the existing legal aughority to operate the Health Sciences Advancement Award program. Each of these offices affirmed that the authority conveyed in the General Research Support statute (P.L. 86-798) was adequate for the action taken.

The Department, as a consequence of these opinions, believes that the requirement of specific statutory authorization for the HSAA program has been met. Thus Recommendation No. 7, which is predicated on a contrary assumption, must be considered as inapplicable.

The Department agrees with the objectives inherent in Recommendation No. 6 that new programs be "formally reviewed by the Department and the Executive Office of the President to determine its conformance to the national education and science policy." The formal process of the development of the budget requests requires both program examination and concurrence by the Department and the Bureau of the Budget. Thus it may be reasonably inferred that this program was in "conformance with national education and science policies."

Single-Instrument Support:
The Sloan-Kettering Award

"Recommendation No. 8.--The committee recommends that the Congress amend this provision of the act to clarify and limit the Surgeon General's blanket authority to adopt 'such additional means as he deems necessary or appropriate' for the conduct and support of research."

To be able to act in exceptional circumstances, and to undertake special arrangements in furtherance of research, not only in cancer but in comparably urgent and difficult health problems, are viewed by the Department as essential provisions of law for the discharge of national responsibilities in the health area.

Thus the Department does not support the Committee's recommendation that Congress amend this provision of the Act with the intention of limiting the authority, now resident in the Secretary of HEW, to undertake such necessary and appropriate action in respect to the conduct and support of research in matters related to health and disease.

Because of the breadth of this authority, however, the Department concurs in the view that it should be exercised only after careful consideration of the circumstances involved. To assure that such careful consideration precedes such action, the formal delegations of authority within the Department are being reviewed to assure that there are appropriate restraints on the use of this authority.

Quality of Research

"Recommendation No. 9.--The committee recommends that the Surgeon General establish a high standard of quality as the basic qualification for research project support, and that he develop adequate procedures for the uniform maintenance of that high standard by NIH and other bureaus of the Public Health Service. The confinement of research grants to projects in the range of excellent to good should not be breached except in special circumstances where the reasons for supporting a lower quality project are fully documented in a written record."

The support of investigator-initiated research projects through the Regular Research Grant programs of NIH is a major and long-standing component of NIH operations. What is expected of the individual investigator under this program of NIH is the sine qua non of science: to propose scientifically meaningful research of the best that he is capable. A scientist can do no less. The selection of such projects for the award of grants is through a process that assigns determinant roles to peer groups, notably study sections and advisory councils. This review system, which derives from the statutory requirement for affirmative advisory council recommendations prior to award, constitutes a truly unique achievement in meshing the considerations of public purpose with the criteria and values of science in the conduct of Federal programs. The process has been subjected to numerous critical examinations and broadly judged to be sound, effective, and conducive to the interests of both science and public.

The standards of this process are rigorous. The result: As the number and dollar value of research grant applications has increased, the proportion of applications surviving this review has fallen. In recent years almost half of all the new and 40 percent of the competing research grant applications received by NIH have failed to pass the basic qualitative threshold and have been disapproved. The following charts show this trend graphically.

The priority scores utilized in the review process are assigned to applications only after they have been approved by a study section. Thus, the scientific merit of a project and its eligibility for NIH support have already been established. The purpose of the priority score is less to quantify quality in an absolute sense than to provide a means of gaining a collective opinion of the reviewers for ranking the applications recommended for payment. This is not to suggest that priority rating is unrelated to scientific merit, but other subjective variables are reflected in these numerical indices. To illustrate: Given two project proposals of corresponding scientific merit, one an epidemiological approach, another a laboratory technique, one reviewer might assign higher priority to the former as a consequence of his conviction that the "state of the art" in that science-discipline calls for more emphasis on epidemiologic studies. Thus, priorities reflect scientific choice

as well as scientific merit.

In 1956 the NIH appropriation for project-grant support was $40 million, which represented 13 percent of the estimated total national expenditure on medical research ($312 million) and involved the support of only 2500 projects. The national need was great and the research capacity of the Nation substantial; national programs were severely limited (partly because of the Korean war); and only established investigations, research programs, and institutions were being supported. The skewing of priority ratings to the upper end of the scale during the period when these conditions were in substantial dominance was inevitable.

Ten years later that universe of medical research was transformed. National expenditures in this area totaled over $2.0 billion, of which the Federal share was $1.3 billion and the NIH figure was $791 million, the predominant share of which was expended in support of almost 16,000 research projects. These are the dimensions of a national medical research effort which is not only of a wholly different order of magnitude, but is beyond equating in respect to the scope and depth of the science involved or the investigators and institutions engaged, and to the extent to which the national interests are being served. To ignore these massive changes and to assume that the priority rating pattern of 1956 is a valid base of comparison with the pattern of 1966 hardly seems reasonable.

Furthermore, it would be difficult, indeed, to demonstrate any meaningful change in the priority character of research grant applications after the initial period of rapid program growth. Thus, since 1960 the distribution of priority scores--as shown by the table printed in the Committee's report--has remained virtually constant with:

- about 24 percent in the 100-199 group,
- about 48 percent in the 200-299 group,
- about 25 percent in the 300-399 group, and
- only 3 or 4 percent in the lowest priority category of 400-500.

In 1966 and 1967 the proportion in the highest priority group has shown a distinct increase, to 26 percent and 30 percent respectively.

As a consequence of its examination of all the considerations surrounding the Committee's comments on the quality of research being supported through NIH programs, the Department concludes, as noted at the outset of this discussion, there has not been a "continued lowering of research standards" in the conduct of these programs nor has "a much lower level of competence . . . replaced high quality as the standard for determining whether research is worthy of Federal support." The available evidence, to the extent that it can be considered to reflect qualitative trends, suggests quite the opposite trend.

Thus, in respect to the Committee recommendation that a high standard of quality be the basic qualification for research project support and that adequate procedures be developed to maintain that standard, the Department believes that the existing arrangements have given and will continue to give firm assurance that only projects worthy of public support for the accomplishment of the statutorily established objectives of NIH programs will be awarded grants.

In respect to that part of the recommendation relating to the circumstances under which projects fall in the lower priority ratings, present procedures require that any application falling in the lowest 10 percent of the priorities assigned by any Study Section be subjected to special review by staff and the relevant Advisory Council before an award is made. This process assures that applications receiving the lowest decile of priority ratings are thus deliberately selected for their importance to some aspect of the relevant Institute's program. This procedure has been in effect since June 1959 in response to criteria set by President Eisenhower.

Concentration of Grants

"Recommendation No. 10.--The committee recommends that the Public Health Service's responsibility for programs designed to develop or improve the capability and resources of educational institutions be limited to medical and other health professional schools. The general research support program is not included in this category since the Congress authorized these grants, permitting broad discretionary spending, specifically to supplement project grants. The committee recommends that the responsibility for grants intended to strengthen educational institutions other than health professional schools be confined to the National Science Foundation and/or the Office of Education--the two Federal agencies broadly responsible for strengthening basic science and education."

A policy that would limit NIH efforts to improve the health-related research capability and resources of educational institutions to medical and health professional schools would not be compatible with the realities of existing Federal-university relationships, nor with the scope of science upon which the advancement of health capability depends.

The last several decades have seen the evolution--principally in non-health professional components of graduate schools--of hybrid scientific disciplines such as biochemistry, biophysics, and biomathematics into strong and viable areas of scholarly endeavor. These new sciences represent points of contact and areas of interdigitation between the sciences of chemistry, physics, and mathematics and that of biology. New knowledge developed in these hybrids, particularly in specific subdisciplines, has proved to be enormously significant for health. There is every reason to believe that fundamental insights into health problems will continue to flow from these sources.

The Department believes that there are important and noncompetitive developmental roles to be played by NIH, NSF and OE in the non-health professional components of this Nation's graduate schools in the present context of national policies and arrangements for support of university functions. OE's mission is the broadest and most general--to support the basic process of graduate education and the basic educational enterprise. NSF has primary responsibility for education and basic research in the sciences generally, including mathematics and engineering. And NIH must focus on research and research training in the sciences related or oriented to health.

Thus, in respect to the Committee's recommendation that NIH's programs directed towards the improvement of the capability and resources of educational institutions in the biomedical area be confined to medical and other health professional schools, this Department believes that such modification would impair the achievement of national objectives in the area of health and medical research in the present context of Federal relationships to educational institutions.

Aiding Weaker Institutions

"Recommendation No. 11.--To provide for more equitable treatment of the smaller and less wealthy institutions, the committee recommends the following changes in PHS policies:

"(1) Qualification for a GRS grant should be based on a school's receiving $100,000 or more annually in research project grants from all units of the Public Health Service combined, rather than exclusively from NIH. Moreover, HEW should consider broadening the GRS program, with appropriate legislative authority, to include health-related research grants made by other units of the Department in such programs as vocational rehabilitation and maternal and child health. Eventually, a single general research support grant for each eligible institution, administered on a Government-wide basis, would be most efficient and desirable.

"(2) The amount of each GRS grant should be determined solely on the basis of the institution's research expenditures from Federal sources. The committee does not believe the premium given for non-Federal research funds under the existing formula operates as a meaningful incentive for attracting private funds. Rather, this premium discriminates against poorer institutions, favors research organizations over institutions of higher education and, as demonstrated in chapter IV, has been difficult to administer and wasteful of Federal research money.

"(3) The same GRS eligibility requirements should be applied to health professional schools as to other institutions. To the extent that health professional schools require assistance in developing a research capability, this should be accomplished by a separate program of technical and financial assistance tailored for the purpose.

"(4) The separate biomedical sciences support grant should be discontinued, and the GRS grant awarded to graduate schools on the same terms as to professional schools, hospitals, and research institutions.

"(5) Until such time as a single general research support program may be established on a Government-wide basis, the NIH program and NSF's institutional grants program should be closely coordinated to avoid duplication. Some institutions

presently receive general research support from both NIH and NSF computed on the basis of the same research projects; this occurs because NSF bases the amount of its award exclusively on the research (as well as some research training) grants it makes, while NIH includes these same NSF research grants in the computation for GRS awards."

As noted in the prior section of this response dealing with General Research Support program, this program was designed to provide support for the health research and research training programs of institutions and thus to complement project support for individuals within those institutions. Its major intents were to provide funds to redress imbalances and inflexibilities created by categorically oriented research-project grants; to foster autonomous institutional growth in the health sciences area through the development of research and research training programs in accordance with self-defined institutional aspiration; and to create and operate the central resources and facilities used in common by many biomedical scientists within the institution.

In evaluating the meaning of "equitable" utilized by the Committee, one should not lose sight of the fact that intrinsically the GRS program is discriminatory. It was intended, within limits, to provide support in proportion to the imbalance or straining of institutional programs by categorically oriented research-project grants from NIH. Institutions were not to receive awards unless a reasonable basis was evident to conclude that such distortion operated. Hence, a threshold, defined in terms of dollar amount of NIH support, became a necessary (but not sufficient) requirement to be met in establishing institutional eligibility.

The intent of these remarks is to introduce a note of caution into the formulation of the concept of "equitable treatment" when applied to the "smaller and less wealthy institutions" under the GRS program.

Thus, in respect to the general purpose of Recommendation No. 11, the Department shares the concern expressed in the Committee report for institutions which are small, or modestly endowed, or outside geographic areas of high-population density. With the Committee, the Department believes it to be in the national interest to upgrade the research capability as well as the general excellence of all classes of institutions of higher learning. However, the Department is persuaded that the fundamental considerations involved in seeking this objective are so different from those toward which the General Research and Biomedical Support programs are directed that, as noted above, a broader national program should be devised for this purpose.

In respect to the specific components of Recommendation No. 11, many of the changes proposed are ones that have been under consideration within the Department. If the Report of the National Academy of Sciences-National Research Council evaluative study of the General Research Support program had not cautioned against such action before at least 1967, and were it not evident that some of these actions, if taken precipitously, would have serious adverse effects on specific institutions, several of these recommendations would have been put in force some time ago.

The Department concurs in principle with the Recommendation 11(1) that the eligibility base for general research support be broadened beyond the present NIH base. Plans for effecting this will be developed within the coming year. With regard, however, to expanding this program to make possible a DHEW-wide and, eventually, a Government-wide general research support program, the Department has misgivings. These derive from the conviction that the changes would inevitably reduce the effectiveness of these funds in achieving the statutory missions of the separate Federal agencies which support research and development efforts in their respective fields of interest in eligible institutions.

The Department concurs in principle with Recommendation No. 11(2), the effect of which is to terminate automatic eligibility for those classes of health professional schools initially declared eligible when the program began in 1962. However, it reserves the right to put this change into effect in such a way as to minimize dislocation and adverse effects in grantee institutions, and further hopes that new authorities and funds will become available to develop research capability and otherwise strengthen some of the previously eligible institutions which need and have no other source of such support. Particular consideration will be given to the problems of these institutions in the legislative submissions that relate to the extension of the Health Professions Educational Assistance Act.

The Department wishes to study more carefully Recommendation No. 11(3), to discontinue the Biomedical Sciences Support Grant program. The view at NIH is that there should be as many fund-allocation formulas as there are homogeneous classes of institutions in terms of institutional importance as a performer of health-related research. It may turn out that no distinctions sufficiently important to warrant separate categorization should be made, in which case the recommendation will be accepted. Alternatively, two or even more programs may appear most appropriate.

The Department concurs in Recommendation No. 11(4) that there be close coordination between NIH and NSF in the evolution of their respective programs of the type that NIH calls general research support. At the moment they are the only sources of Federal support for such programs. It should be noted that coordination has been practiced in the past, even though differences of opinion--which the NIH believes to be entirely appropriate--on some problems continue to exist.

As noted in response to Part 1 of Recommendation No. 3, this Department has directed PHS and NIH to submit to the Secretary a plan for the modification of the formula utilized for calculating the awards under the General Research Support Grant program which provides for the elimination of the premium factor for non-Federal research expenditures, as well as other changes considered desirable, to be effective with the GRS awards made for fiscal year 1969.

This plan will also take into account the foregoing recommendations of the Committee.

Training Grant Programs

"Recommendation No. 12.--The committee recommends, further, that the Secretary of HEW review the numerous NIH and other PHS training grant programs to determine if they are effectively organized to serve national manpower needs and objectives. This review should be concerned particularly with ascertaining if the institutions which receive large amounts of training funds are making a proportionate contribution to the nation's manpower supply. Conversely, the Secretary should determine if training grant policies discriminate against schools which award graduate degrees in the biomedical sciences but receive little or no PHS training support."

NIH training programs provide support for both predoctoral and postdoctoral training in the biomedical sciences. Approximately 65 percent of the support covers predoctoral training, with heavy emphasis upon the basic medical sciences, and about 35 percent covers postdoctoral training. Because of the inclusion of this significant postdoctoral training component, there is not necessarily a 1-1 correspondence between NIH training support and doctoral output in the basic medical sciences.

NIH training grant support is provided not only with respect to the intrinsic scientific quality of institutional programs, but also in terms of the relevance of the proposed training to the authorized mission of the awarding NIH Institute. It is not possible, therefore, for NIH training grant support to be provided to every environment simply because it awards advanced degrees in the biological sciences. Rather, training grant awards must continue to be made selectively on the basis of the twin criteria of scientific excellence and NIH mission relevance.

Nonetheless, the Department concurs with the Committee's view of the importance of assessing the effectiveness of NIH training programs in meeting urgent national needs for biomedical research manpower. Thus, in respect to Recommendation No. 12, the Department is directing the National Institutes of Health to extend its already broad and thorough review of the biomedical research manpower area now under way. The findings and conclusions of these studies are expected to be available during the forthcoming year. A subcommittee on manpower of the Advisory Committee to the Director of NIH has recently been established to provide guidance in the review of NIH training programs. It is anticipated that the advice and recommendations emanating from this group will also be of significant value in determining the appropriate NIH training role and responsibilities in the years ahead.

Technical Assistance to Institutions

"Recommendation No. 13.--The committee recommends that the President designate one or more Federal agencies to provide technical assistance, upon request, to help institutions plan for the improvement of their science education and research programs. It would be logical for the Public Health Service to be concerned with the health professional schools; other groups of institutions in which the biomedical sciences are taught might be made the responsibility of the National Science Foundation and/or the Office of Education."

While deferring to primary concern of the Executive Office of the President in respect to this matter, the Department wishes to emphasize that it has actively supported and participated in interagency efforts to this end and will continue to do so.

In respect to Recommendation No. 13, the Department feels that sufficient preliminary steps have already been taken by the Executive Branch so that it should be possible, within a reasonable period of time, to designate specific "cognizant agencies" for providing technical assistance in the development of academic science capabilities in respect to particular categories of institutions or areas of research. However, it is felt that it would be premature, pending the further development of these concepts, to make the division of responsibilities for the biomedical sciences suggested by the Committee.

## Improving the Academic Quality of Graduate Institutions

"Recommendation No. 14.--The committee recommends that the President give early attention to the problem of improving the academic quality of weaker graduate institutions and that a unified and coordinated Federal assistance program be developed for dealing with this matter. The committee believes the present piecemeal and uncoordinated approaches of Federal agencies to institutional improvement are competitive, wasteful, and frequently not directed to the heart of the problem."

Again the Department acknowledges the principal concern of the Executive Office of the President with this recommendation, and thus comments only from its more limited purview.

Graduate education is the culmination of the formal process of equipping individuals with the requisite scholarly capability for independent teaching, research, and technical endeavor at the frontier of expanding knowledge and technological innovation. As a consequence of the evolution of this academic function over the past 50 years, the graduate schools of the United States now encompass a predominant portion of the intellectual force of the Nation. This Department is convinced that only through the careful cultivation of this resource can the Nation be assured of continuing capability to advance knowledge, to extend the base for technological progress, to influence the social, cultural, and economic quality of national life, and to exert intelligent and effective leadership in world affairs. Gaining a national consensus on this fundamental circumstance constitutes the major challenge to Legislative and Executive efforts to bring about a more rational relationship between the Federal Government and graduate education.

Thus, in respect to Recommendation No. 14, the Department shares the Committee's concern with the problem of improving the academic quality of weaker graduate institutions. The Department emphasizes, however, that the existing circumstances are not solely the consequences of the diffusion of Executive responsibility in this matter, but are basically reflective of the yet ambivalent and indecisive state of the national mind in respect to the manner in which national action in this area will be taken and the policies which should govern. Nonetheless, a considerable effort is under way within the Executive Branch to improve existing conditions and to further the resolution of national policy in this area.

Central Management of Grants

"Recommendation No. 15.--The committee recommends that the Surgeon General (1) establish in PHS, and in each of the bureaus which administer grant programs, a single grants management office to provide uniform interpretations of policies and procedures, and (2) provide adequate staffing for PHS's Division of Grants and Contracts to enable this unit, on a current basis, to maintain surveillance over and liaison with the several bureau grants management offices to assure that policies are being properly and uniformly implemented."

In the initial section of Part II of this commentary, there is a review of the major efforts within NIH, PHS, and at the departmental level to advance the status and capability of the grants management function. The Department believes that substantial progress has been made in this area and that the framework is considerably stronger today than in the past. The Department would also re-emphasize its previous statement that there is no disagreement in respect to the responsibility that bears upon the Department and its constituents for sound management of grant programs.

Without question, an increase in competent grant management staff and further progress in the coordination of the necessarily diverse activities is required. Thus, in respect to Recommendation No. 15, the Department is in full accord with the objectives sought. The planned reorganization of the health functions of the Department now under study will provide both the opportunity and the means to focus and strengthen further the grant management activities of each of the constituent agencies.

Advisory Committees

"Recommendation No. 16.--The committee recommends that appointments to advisory councils be limited to one 4-year term, with members ineligible for reappointment, or appointment to other advisory councils, for a period of 4 years following the completion of their terms.

"The committee recommends further, that consideration be given in the selection of advisory committees to obtaining a balanced representation of geographic regions and educational institutions. To the extent possible, consultants should be drawn from among qualified scientists who are not themselves recipients of PHS grants."

The National Advisory Councils are unusual, if not unique, in that they are not only established by law but have the statutory authority to make recommendations prerequisite to the award of a grant by the Surgeon General. These Councils provide the basic mechanism for broad public participation in the programs of NIH. This unusual framework for joining non-Federal advisers in the direct conduct of Federal programs has been remarkably productive and has achieved complete acceptance by the scientific community. Indeed, much of the rate of growth, scientific distinction, and public appeal of NIH programs is directly attributable to this engagement of both lay concern and technical competence in program affairs.

Eligibility for reappointment, which is the subject of the Committee's recommendation for change, is covered by statute: reappointment of a member to the same Council is prohibited for one year following completion of a term of service.

Thus, in respect to Part I of Recommendation No. 16, the Department recognizes the need for rotation of membership on National Advisory Councils as the best means for insuring that interplay of fresh and disparate viewpoints which will result in benefit, not only to NIH programs, but also to the national understanding and the exercise of national responsibility. A tightening of requirements for reappointment would be consistent with current committee management practices at NIH, which are now based on a limitation prescribed by law. At the same time, such modifications should be kept in balance: undue restrictions upon membership could result in denying access to the experience of advisers familiar with the diversity of NIH missions, with the operation of this complex system, and with the officials whom they are advising. Consequently, the selection and appointment procedures for

National Advisory Council members are being revised to provide for special review of all recommendations for reappointments to assure that such reappointments are made only when there is clear evidence that the national interest is served thereby.

The selection and appointment of members of technical advisory committees present a different set of considerations. The maintenance or enhancement of ability to judge the scientific quality of proposals is paramount. Candidates for appointment are therefore selected primarily on the basis of outstanding qualifications as investigators in clinical or laboratory research. Because this review system is designed to assure the maintenance of scientific merit in the projects supported, it thus demands that its membership be selected on the basis of competence.

Thus, in respect to Part II of Recommendation No. 16, the Department must emphasize that the first requirement for selection of technical advisors is excellence in a specific field of research. Since excellence in science and medical research is not equivalently distributed in all States and all institutions, a proportionate representation in the distribution of PHS technical advisors by State and institutions cannot be expected. Inevitably the distribution of Federal support in mission programs follows the distribution of competence, which in turn forms the universe from which technical advisors must be selected. There appears to be no reasonable escape from this dilemma. To the maximum extent possible, the Department will endeavor to assure the broadest representation in the selection of technical advisors consistent with the basic obligation of serving the primary statutory objectives involved.

Institutional Accountability

"Recommendation No. 17.--The committee recommends that the percentage of grant funds allocated to the general research support program not be increased, and no new forms of institutional support be initiated, until (1) PHS has modified GRS policies for a more equitable and efficient distribution of these funds, as recommended earlier in this report, and (2) PHS or HEW is prepared to promulgate grants management standards and to determine that institutions wishing to be eligible for research support are in compliance with those standards."

Without question, the grant relationship imposes upon the grantee clear responsibility for the effective management of the funds awarded in the accomplishment of the purpose for which the grant was made. The statement of principles governing the use of grant funds by grantee organizations promulgated by PHS makes this fundamental condition clear. Thus the Department is in full concurrence with the objectives being sought in the committee's discussion of the problems of institutional accountability.

The matter of concern for the Department that arises in connection with the Committee's discussions of institutional accountability is the implication that the recipient of a grant, to meet the obligation for prudent management, is required as an absolute condition of support to give evidence of the existence within the grantee institution of formal management systems utilizing modern accounting and auditing, central purchasing, inventory management, and other basic business techniques. As the Committee is well aware, authority to make grants involves an explicit Act of Congress. Thus, the grant is viewed as a special instrument of public action. It is distinguishable from a contract in that it does not constitute the procurement of goods or services required for the performance of public business. In contrast, it is a unilateral act centered in the concept that the public interest will be served by contributing to the work of a non-Federal organization. Thus the primary concern in making a grant is the identification of the public value to be gained through the grant and the capability of the awardee to advance such value. The determination of whether the public interest has been so served is not in the nature of the expenditure that is made under the grant, but the degree to which the broad objective being sought has indeed been furthered by what was accomplished as a consequence of the award.

In respect to Recommendation No. 17, however, the Department is convinced that it would be unwise to establish any absolute degree of management capability on the part of a grantee institution as an explicit condition of eligibility for research support. This must continue to be a variable judgment encompassing both the nature of the public purpose to be served and the assessment of this Department of the capability of the institution for prudent use of the funds involved. This view, however, will not diminish the efforts of the Department and its constituents to contribute to the managerial capability of the framework of non-Federal institutions upon which the progress of its grant programs depends.

TOTAL AUTHORIZED PERSONNEL IN NIH

Mr. NATCHER. Dr. Shannon, what is your total authorized personnel in NIH?

Mr. SEGGEL. Sir, we have a ceiling of 10,680 for full-time permanent positions and 719 for other types of employment, a total of 11,399.

Mr. NATCHER. 11,399. How many vacancies do you have at the present time?

Mr. SEGGEL. We had 298 vacancies, for all types of employment as of February 29, 1968, but we have commitments which should reduce that figure substantially by the end of April or early May.

Mr. NATCHER. How many new people are you requesting for fiscal year 1969?

Mr. SEGGEL. We are requesting 664 new positions, sir.

POWERS AND RESPONSIBILITIES OF SURGEON GENERAL AND DIRECTOR OF NIH

Mr. NATCHER. Dr. Shannon, as you know, I have only been a member of this subcommittee 1 year. I have served as a member of the Appropriations Committee now for nearly 15 years. What does the basic legislation provide as to NIH and the Surgeon General? What is the setup Dr. Shannon?

Dr. SHANNON. That is a very complicated question.

Mr. NATCHER. Mr. Kelly, maybe you could help us.

Mr. KELLY. Yes, sir; the Public Health Service Act creates the Public Health Service as an operating agency of the Department of Health, Education, and Welfare. By the reorganization plan which the Congress adopted last year all of the powers and duties and responsibilities of that act were placed in the hands of the Secretary and then he in turn delegates the responsibilities to carry out the Public Health Service Act to the extent that he sees fit, and these are presently delegated through the Assistant Secretary for Health and Scientific Affairs to the Surgeon General, who carries them out with certain reservations where the Secretary has to act.

The Surgeon General has organized the PHS into several bureaus and one of these, the principal research arm of the PHS is the National Institutes of Health, headed by the Director. He in turn has been delegated by the Surgeon General the preponderance of the powers to carry out the medical research program including the approval of research grants, training grants, et cetera.

Mr. NATCHER. Is the Surgeon General responsible for NIH Mr. Kelly?

Mr. KELLY. Yes, sir.

Mr. NATCHER. As Surgeon General the American people naturally expect this particular individual to deliver to the people the results of research and all of the accomplishments of the Department of Health, Education, and Welfare as it pertains to the health of the people would you say, Mr. Kelly?

Mr. KELLY. I think that is a fair statement.

Mr. NATCHER. How many Secretaries have we had, Mr. Kelly?

Mr. KELLY. Seven.

Mr. NATCHER. Have we ever had a good hardheaded businessman who was an excellent administrator?

Mr. KELLY. Yes, sir; I think we have had several. An outstanding

example of such a businessman was Marian Folsom, who served as the vice president and treasurer of the Eastman Kodak Co.; came to Washington as the Under Secretary of the Treasury; and then was made Secretary of the Department of Health, Education, and Welfare.

Mr. NATCHER. The reason Dr. Shannon, why I ask these questions, I find a number of people very much concerned about the Department of Health, Education, and Welfare from the standpoint of being a department in our Government that is not manageable. On the opening day of our hearings this year we were informed that 94 percent of the total amount appropriated for HEW is for grants.

GROWTH OF NIH BUDGET

Dr. Shannon, how long have you been Director of NIH?

Dr. SHANNON. Approximately 13 years, sir.

Mr. NATCHER. Who was ahead of you?

Dr. SHANNON. Dr. Sebrell.

Mr. NATCHER. That was the year——

Dr. SHANNON. The summer of 1955.

Mr. NATCHER. In the year 1955 the appropriation——

Dr. SHANNON. This would be fiscal 1956 we were in then.

Mr. NATCHER. What was the amount of the appropriation that year?

Dr. SHANNON. $98 million.

Mr. NATCHER. To be exact, it was $98,458,000. That is pretty close. Your request at this time as I understand is $1,196,693,000.

Dr. SHANNON. Yes, sir.

Mr. NATCHER. In 1953, the amount appropriated for NIH was $59,030,750. In the year 1960, the amount appropriated was $400 million.

The overall amount for fiscal year 1968 was $1,178,924,000. Is that before or after House Joint Resolution 888?

Mr. SEGGEL. The figure $1,178 million, did you say?

Mr. NATCHER. I am reading from the justification; $1,178,924,000.

Mr. SEGGEL. That is the appropriation, sir, before the reduction.

Mr. NATCHER. Before House Resolution 888.

Mr. SEGGEL. Correct.

Mr. NATCHER. What is the exact amount of reduction under that resolution?

Mr. SEGGEL. As I mentioned before, the general reduction that was made in our budget amounted to about $60 million, of which $6 million was in personnel, and travel and related expenses. We had about a $12 million reduction in construction and about $31 million in regional medical programs, both of which really are carryovers. In other words, those are balances being carried over—not taken away but carried over to the following year.

Mr. NATCHER. Now, Dr. Shannon, in your statement to the committee, you stated that the budget estimate for fiscal 1969 are spartan in character. You really believe that, too, don't you, Dr. Shannon?

Dr. SHANNON. Indeed I do, sir.

BUDGET INCREASES BY ACTIVITY FOR 1969

Mr. NATCHER. Where are your major increases, Doctor?

Dr. SHANNON. I can give you a rundown on them in summary form.

We can give them to you by Institute or activity.

Which would you prefer?

Mr. NATCHER. Let's take it by activity and give us your major increases if you will, please.

Dr. SHANNON. The largest increase would be for the regional medical program grants which increases by $44.9 million. Other grant increases, that is for research grants, fellowships and training—the aggregate increase in these collective items is $75 million.

In the category of direct operations, there is an increase of $5.8 million in laboratories and clinics, the direct operation at Bethesda; $9,590,000 in collaborative research and development. This is in areas largely of a contract nature. For other direct operations, which includes program direction, review and approval, and a whole variety of things, the aggregate is $3 million. This gives a total increase in new obligational authority of $93,667,000. That is offset by one large cut in research facilities construction which shows a reduction of $17,800,000. We were talking to Mr. Laird about it a short time ago.

By Institute or by operating divisions, the largest single increase is the regional medical program, again. The aggregate increase of all other operating divisions is $47.6 million. Again, this is offset by a reduction of $17.8 million in research facilities construction.

Mr. NATCHER. Those are your major increases for fiscal year 1969?

Dr. SHANNON. Yes, sir.

### NIH APPROPRIATIONS RETURNED TO THE TREASURY

Mr. NATCHER. Dr. Shannon, is it true that for a number of years you had more money than you knew how to handle?

Dr. SHANNON. No, sir, we did not have more money than we knew how to handle. We had more money that we felt could be spent prudently, and we did not spend it.

Mr. NATCHER. Dr. Shannon, what years did that take place? Was that during the period, Dr. Shannon, beginning along about the calendar year of 1959, 1960, 1961?

Dr. SHANNON. That was primarily 1961, 1962, and 1963, I think. I would refer to 1962, 1963, and 1964. Those were the years where we felt we could not effectively and prudently spend the moneys made available.

Dr. NATCHER. Now, Dr. Shannon, how much was involved?

Dr. SHANNON. In 1962 we returned to the Treasury $69.7 million; 1963, $90 million; 1964, $34 million; 1965, $5.6 million; 1966, $11 million, and in 1967, $23 million.

One complicating factor I must here point out: Not infrequently these appropriations were made very late in the year, so with substantial increases we had scarcely 6 months, and in some cases less than 6 months, to develop a program.

Secondly, these programs having been increased primarily by congressional action rather than by prior, staff-developed proposals meant we had to staff and develop them during a short period of the year.

I think that in many of those cases where we returned very substantial sums it was because we could not program those in the limited time available. We preferred not to spend simply because funds were available.

Mr. SEGGEL. In the last 3 years our balances have been what could be termed "normal balances." In other words, 1 percent of the total available to us.

Last year it was $23 million but, of that, $12 million was a carryover for the regional medical program which was a new program just getting underway.

Mr. KELLY. I would like to underscore what Dr. Shannon says about the time period available. You not only have an appropriation coming in September, October, or November, but in each instance where the Congress made a large increase, considerable discussion occurred between the Public Health Sevice and the Secretary, between the Secretary and the Bureau of the Budget and the President, on the method of using the funds and on a justification of how they will be applied so that when the Director of the National Institutes of Health was authorized to proceed with the expenditure of those funds, it was more nearly January 1 than it was at the beginning of the fiscal year.

One of the things that I think we take a great deal of pride in is, during this period of the very rapid growth and availability of funds, that repeated studies demonstrated that the level of quality of the research that was supported was not reduced and that it was preferable to return the funds unused rather than to lower the quality of the research that was supported.

Mr. NATCHER. Dr. Shannon, one of the matters that concerns me, as a Member of this Congress, is the fact that a number of outstanding doctors—like you, Dr. Shannon—doctors who are taxpayers and who are very much interested in the health of our people and in the successful operation of NIH and the Department of Health, Education, and Welfare generally, they are very much concerned about the way a lot of this money is being expended. I say that to you frankly. They are very much concerned about it. Good men; good doctors; taxpayers. People who are just as concerned with improving the health of the people as you and the members of your staff and who are as much concerned as anyone on this side of the table. Dr. Shannon, they are very much concerned about it.

### AMA REPORT ON NATIONAL INSTITUTE OF HEALTH

Dr. SHANNON. Could I answer that equally frankly? I fully appreciate this. I would point out that this concern has resulted in a substantial number of studies by very responsible groups. The most recent one was none other than a study sponsored by the board of trustees of the AMA. It was undertaken by the AMA primarily because they felt that these funds were not being well spent and that there was overexpenditure in support of research, to the detriment of other programs.

This study was conducted by a group of people who started off with the conviction that this was not a properly managed program. I would be very glad to make available to you—I don't have it with me—the report of this committee to the house of delegates. They reached quite a contrary opinion.

Mr. NATCHER. Dr. Shannon, it would be of assistance to me, and I think the other members of the committee, if you would have one of the members of your staff break that down. We don't want to clutter this record up. If you would have it broken down and digest it some-

what so that we could insert it in the record, unless there is some objection, at this point.

Mr. LAIRD. I think that is a good idea. I was at the house of delegates meeting when the report was submitted and it is a very interesting report.

Mr. NATCHER. I think it should be included at this point in the record and, Dr. Shannon, have it broken down and summarized.

(The information requested is as follows:)

AMA REPORT ON FEDERAL RESEARCH SUPPORT

A commission on research was set up by the American Medical Association in 1963 to examine—

1. The impact of Federal research grants on (*a*) medical education; (*b*) the institution involved; (*c*) the Nation's scientific and technical resources;

2. The effect of the expanding Federal research role on the broad areas of medical service outside of medical education;

3. The effect of Federal spending on private giving and the ability of the latter to make a meaningful contribution; and

4. The scope of Federal medical research support and the mechanisms used.

Although the commission, in its early hearings, expressed grave misgivings about the growth of Federal support for medical research, the first two recommendations in the commission's report, issued 3 years later, are that:

"1. The American Medical Association should support in general the Federal biomedical research program * * *," and that

"2. The programs of the National Institutes of Health should be recognized for their contributions to the national biomedical research effort."

Indeed, in the body of the report the commission comments that the NIH has been sensitive to the values of academic freedom and the issues of control. Its administrators have been more understanding and flexible in their administrative approaches to medical schools than many private donors and officials of State or local governments. Top level Federal administrators have often been more perceptive of the issues of academic freedom than have been many academic administrators.

The report's principal conclusions can be briefly summarized. With respect to the "impact of Federal research grants on medical education" the commission concludes that Federal grants have, on the whole, had beneficial effects on the medical schools. However, "imbalances have developed among the interrelated areas of research, teaching, and patient care in some medical school faculties and in some teaching hospitals * * * caused by burgeoning financial support for research—in the midst of a relative scarcity of funds for educational programs." The commission agrees that while "several developments * * * point to the possibility of increased Federal control * * * the current modest institutional grants * * * have had a salutary effect in restoring at least some measure of institutional control." However, "the policy of the Congress that universities and medical schools must share in the overhead cost of research projects has imposed difficulties upon many academic institutions," and "the techniques of direct Government support of some investigators * * * and the predominant use of project grants * * * have created problems in most medical schools."

After examining the "effect of the expanding Federal research role on the broad areas of medical service outside of medical education," the commission concludes that, in future, the research projects with the greatest influence on medical service will be "those relating to the development of new methods in the provision of health care and the administration of health services."

Private funds continue to contribute significantly in the support of research programs. Even though research programs supported by voluntary health organizations are similar to those funded by the Federal Government, the commission believes that the "best interests of science and medicine and of the public generally would be served by maintaining a pluralistic support of biomedical research."

The commission recommends, inter alia:

1. That the AMA should support the Federal biomedical research program but should play the role of responsible critic as well as sympathetic advocate;

2. That the AMA should award grants to selected institutions to enable them "to initiate or enlarge their research programs" thereby encouraging "better geographical distribution of 'centers of research excellence' ";

3. That "membership on NIH study sections [and advisory councils] should provide for a sufficient rotation to insure continuous infusion of new blood";

4. That responsibility for fiscal accountability should be vested in the educational institutions whose administrative capabilities should be strengthened;

5. That the AMA should support the delegation of "more decisionmaking responsibility for biomedical research from NIH to participating research institutions" and "to this end, increased use of the 'institutional grant' and of the 'program grant' should be actively supported";

6. That "research in the delivery of health care is of great importance and should be encouraged";

7. That the imbalance between research and education in the medical schools be remedied; and

8. That the current Federal patent policy, which the commission believes to be "hampering" research progress, should be altered and that the "basic principles presented by the pharmaceutical industry on June 1, 1965, before the Subcommittee on Patents of the Senate Judiciary Committee should be endorsed."

The members of the commission were:

Hon. Charles E. Whittaker
Former Justice of the Supreme Court

Dr. Robert C. Hardin, dean, State University of Iowa College of Medicine.

Dr. Irvin E. Hendryson, member of the board, AMA.

Dr. Richard L. Meiling, dean, State University of Ohio College of Medicine.

Mr. Thomas W. Phelps, investment counselor.

Dr. Raymond M. Rice, vice president, Pharmaceutical Manufacturers Association Foundation.

Dr. William R. Willard, vice president, University of Kentucky Medical Center.

Dr. David A. Wood, director, Cancer Research Institute, University of California Medical School.

The "Summary of Conclusions" and "Summary of Recommendations," as they appear in the report are as follows:

SUMMARY OF CONCLUSIONS

I

Responsive to the board's first charge to the commission to determine "the impact of Federal research grants on (a) medical education; (b) the institution involved; and (c) the Nation's scientific and technical resources," the Commission concludes that—

1. The Nation's great scientific and technical resources have been enormously expanded in the area of biomedical research since World War II and particularly in the last 10 years as a result of leadership and emphasis provided by both the Executive and Legislative Branches of the Federal Government and resulting financial support. We concur in the general belief that the current level of adequacy and excellence of our biomedical research resources has never before been equaled, although it is probable that the abundant Federal funds for research have inescapably supported a measure of mediocrity as well as the Nation's best in scientific medical talent (ch I).

2. Federal support of biomedical research has become a permanent element of our Nation's policy. This support is responsive to popular demand that the conquest of disease and the betterment of the condition of man become national priorities (ch I).

3. The support of biomedical research has had a profound impact on medical schools, favorable in many respects, adverse in some, and complex in most. On the whole, medical school programs have been enriched through support of research activities. Furthermore, without the system of grants which has evolved in recent years, many medical schools would have been in danger of collapse, and biomedical research and educational programs would have been jeopardized. The most critical source of difficulty has been that support of the total responsibilities of medical schools has proceeded

unevenly so that imbalances have developed among the interrelated areas of research, teaching, and patient care in some medical school faculties and in some teaching hospitals (ch I).

4. The heavy infusion of research dollars, particularly through selected faculty members and departments and independent research institutes and facilities, has glamorized research activity and contributed to a "flight from teaching" of individual investigators (ch I).

5. The commission's most important conclusion with respect to its first charge is: The adverse effects of Federal research grants on medical schools arise from many sources. Primarily they arise from the imbalance caused by burgeoning financial support for research—in the midst of a relative scarcity of funds for educational programs (ch I).

6. All the principal source of biomedical research support, the National Institutes of Health has commendably avoided using its vast powers to influence academic decisions. Nevertheless, the principle still holds that a preponderance of Federal support tends in the long run to lead to Federal control. In the past few years, several developments have occurred which point to the possibility of increased Federal control over the purposes for which Federal research funds are to be used and over the manner in which they are expended (ch II).

7. The past rate of growth of support of biomedical research has not recently been maintained. Meanwhile the increasing cost of research has imposed a squeeze on available funds and thereby tightened competition for them. Within the past several years, the costs of supporting an investigator have doubled. Research proposals are becoming more sophisticated while equipment is becoming more complex and expensive. The net effect of these changes is to compel the establishment of priorities for funds and to increase the demand for accountability (ch II).

8. The study section arrangement organized by the NIH for review of proposed project grants through panels of outside academic experts (or peer groups) has been successful in identifying and supporting research of quality (ch. II).

9. The policy of the Congress that universities and medical schools must share in the overhead cost of research projects has imposed difficulties upon many academic institutions. The policy of requiring the schools to share overhead costs, even though their shares may be relatively small, has been intended to insure that schools participate only in research that is deemed to be of such importance to the school's program that it is willing to commit some of its funds to the project. In view of the large volume of Federal research now conducted in the medical schools, however, with the prospect that this may increase in the future, and in view of the hardly sufficient funds available to the schools to pay the cost of their basic operations, this cost-sharing policy diverts institutional non-Federal dollars to research that are needed, and otherwise would be used, for teaching programs (ch. IV).

10. The current modest institutional grants to schools for independent allocation by the schools to their own faculty researchers have had a salutary effect in restoring at least some measure of institutional control. Several investigative bodies and many distinguished leaders are now urging—and we concur—that a higher percentage of the Federal research moneys now going into project grants be shifted to institutional grants and that this money be administered by and in the discretion of the medical schools (ch. IV).

11. The emphasis on project grants has enriched the research capability of the more affluent schools, which are more abundantly endowed with distinguished investigators and both Federal and non-Federal funds, while leaving the other schools relatively poorer (ch. II).

12. The techniques of direct Government support of some investigators, albeit through the administrative machinery of the university, and the predominant use of project grants for supporting research have created problems in most medical schools. Particularly, they have tended to create divided loyalities and disruption of administrative authority (ch. IV).

13. It is widely recognized that the medical schools and their parent universities must share responsibility for whatever imbalances now exist, due to their failures to define their objectives and roles and to develop management capability commensurate with the complex relationships brought about by their federally financed expansions of activity (ch. IV).

II

The second charge to the Commission was to determine the effect of the expanding Federal research role on the broad areas of medical service outside of medical education. The conclusions of the Commission are—

14. The improved quality of patient care currently available reflects, to a significant degree, the expanded research knowledge created in the last decade (ch. I).

15. The prevailing patterns of disease have been changed profoundly by research progress. Advances in immunization and antimicrobial therapy, as well as public health innovations, have reduced many communicable diseases to controllable levels. Longevity has increased, neonatal mortality can be expected to continue its decline, and other health indexes are showing similar progress (ch. 1).

16. The research projects that will have the most important effects on medical service, certainly in the immediate future, are those relating to the development of new methods in the provision of health care and the administration of health services. These projects involve the study of the roles of different members of the health care team, the economics of health care, the role of the medical center in the health care complex, and the coordination and regionalization of health care services (ch. I).

III

The third charge to the Commission was to determine the effect of Federal spending on private giving and the ability of the latter to make a meaningful contribution. The Commission's conclusions relating to that charge are:

17. All sources of support of biomedical research, governmental, private foundation, and industrial, have increased in recent years. Nongovernmental support would be considered significantly increased were it not for a much sharper relative increase of Federal funds for research. Consequently, the sheer preponderance of Federal support has made academic institutions primarily dependent on a single main source, with implications for loss of local autonomy (ch. III).

18. Notwithstanding the sharp reduction in the ratio of private giving to Federal giving, private foundations still can make significant contributions by providing funds for talented investigators who, for one reason or another, do not receive Federal support and by making funds available for those unique and unusual projects which may not be endorsed by peer groups (ch. III).

19. With relatively few exceptions, major voluntary health agencies have tended to support research programs which parallel those funded with Federal dollars and to support many of the same investigators who receive Federal grants rather than assuming unique roles of independent initiative. Some who review the allocation of voluntary health agency grants also review the allocation of Federal support grants. Some voluntary health agencies have tended to overlook or ignore their roles as independent critics of Federal programs, as innovators, and as risktakers. Voluntary health agencies can make unique contributions in each of these areas (ch. III).

IV

The fourth charge to the Commission was to determine the scope of Federal medical research support and the mechanisms used. As this charge is informational, it is covered in the supporting body of this report.

V

The fifth charge to the Commission was to make such further conclusions—which the Commission shall deem advisable for inclusion in this report.

20. The best interests of science and medicine and of the public generally would be served by maintaining a pluralistic support of biomedical research. That is, there should be a diversity of sources of support with a diversity of judgments entering into the allocation of support. Thereby, institutions are more likely to retain their independent identity and their freedom of judgment (ch. III).

21. Progress in the development of new agents for the diagnosis, preven-

tion, and treatment of disease is, we believe, hampered by current Federal patent policy. The problem arises because pharmaceutical companies, universities, and others are in danger of losing all of their investments and ensuing patent rights if and when any use, however nominal, of Federal funds can be traced into the discovery or development of a new product. To protect their interests, sources of nongovernmental research have been tending to avoid the normal interplay of their scientists with federally supported academic scientists (ch. III).

### Summary of Recommendations

In light of the foregoing and in response to the Board's fifth charge to make "such further conclusions and recommendations (as) the Commission shall deem advisable," the Commission makes the following recommendations to the Board of Trustees:

1. The American Medical Association should support in general the Federal biomedical research program. However, because in the public mind research tends to become enshrouded in such an aura of divinity as to exclude critical discussion and analysis of all that is advanced in its name, the AMA has an obligation to the public and to the medical profession to question any facet of the Federal biomedical research program which it may believe to be ill-advised or which it believes to be in need of constructive counsel (ch. I).

2. The programs of the National Institutes of Health should be recognized for their contributions to the national biomedical research effort (ch. I).

3. The Council on Medical Education of the AMA, in cooperation with other interested organizations, should be asked to make additional and progressive studies on the effects of research grants on teaching in medical schools. It should seek and recommend means for providing enhanced status and rewards for excellence in teaching (ch. I).

4. The AMA should support responsible action designed to make available to selected schools of good potential, which have not developed adequate research establishments, special development funds to initiate or enlarge their research programs. These grants should also foster better geographical distribution of centers of research excellence among medical schools and universities (ch. II).

5. The AMA should urge that the purpose of grants be identified precisely so that the Congress and the Nation may know, with reasonable certainty, what is being supported, as a basis for future decisionmaking (ch. II).

6. To strengthen the review mechanism, membership on NIH study sections should provide for a sufficient rotation to insure continuous infusion of new blood and to prevent the development of a monolithic, elite, decisionmaking "establishment." The same principles of rotation should apply to the Advisory Councils of the NIH. While due attention should be given to such factors as geographic distribution, the main consideration in appointing members to the Advisory Councils should be professional attainment and eminence of judgment (ch. II).

7. A new statutory mechanism of overall review and counsel, in an advisory relationship to the Director of the National Institutes of Health, should be established in order to assist in overall program planning and to provide additional checks and balances on program decisions. Membership on this advisory group should consist of men and women of demonstrated professional eminence and judgment.[1] We believe the advisory body should have independent status, under law, to assure that its recommendations and actions will have their intended impact regardless of changes in administrative leadership (ch. II).

8. Accountability for disbursement of public funds should be maintained, but this accountability should depend primarily on strengthening of administrative capabilities of educational institutions (ch. IV).

9. The AMA should urge and support legislation providing for Federal reimbursement of all allocable institutional costs of research projects authorized and funded by the Federal Government (ch. IV).

10. The AMA should urge and support legislative and administrative action designed to shift more decisionmaking responsibility for biomedical research

[1] The Commission notes that the Director of the NIH has, subsequent to the first drafting of this recommendation, created such an advisory body by administrative action. The Commission commends the Director for this move.

from NIH to participating research institutions. To this end, increased use of the "institutional grant" and of the "program grant" should be actively supported. Developments relating to, or affecting, the mix of institutional, program and project grants to academic institutions should be carefully and continuously studied and analyzed for future guidance (ch. IV).

11. The AMA, in cooperation with other interested organizations, should conduct workshops and seminars of academic and medical school leaders and of those Federal administrators who grant and administer Federal research funds, to review mutual responsibilities and relationships, to conduct discussions of developing problems, and to develop new techniques for the better use and management of the vast Federal funds now being made available (ch. IV).

12. Because of the rapid changes which are occuring in the organization of medical practice and the financing of health care, research in the delivery of health care is of great inmportance and should be encouraged, provided it is conducted under proper auspices in accordance with sound research design and methodology (ch. I).

13. The imbalance between biomedical research and education, caused by the heavy, but desirable, Federal support of research, should be corrected by supporting measures that will materially increase both private and public funds for the support of the educational programs of the medical schools. First, among these measures, a more liberal income tax treatment should be allowed to the donors of private funds for medical education, to create increased incentives for them to contribute to medical education. Second, there should be allotted a greatly increased amount for operational expenses of medical schools, to be matched by those schools through private or local governmental sources. Every effort should be made to keep the Federal contribution on a supplemental basis, and the AMA should not support legislation that fails to do so (ch. III).

14. The basic principles presented by the pharmaceutical industry on June 1, 1965, before the Subcommittee on Patents of the Senate Judiciary Committee should be endorsed, namely:

(*a*) Provision should be made, in substantially every case, for the grant or license of exclusive rights in a scientific medical discovery to some industrial concern to assure that drug inventions, even if resulting in some part from Government-financed research, are really developed and made commercially available to the people.

(*b*) When Government funds have solely or primarily developed the invention, it is equitable and rational for the Government to hold the proprietary rights to the invention and to receive reasonable royalties from a licensee, or from licensees, who will manufacture and commercially market the invention.

(c) Where Government funds did not solely or primarily produce discovery and development of the invention, the cooperating contractor-developer alone should have the proprietary rights in the invention (ch. III).

15. The Board of Trustees should provide for a continuing watch, and review of developments in the areas studied by its Commission on Research (ch. IV).

Dr. SHANNON. I think the above was a very good study, conducted by a former Associate Justice of the Supreme Court. There were administrators in medicine and people practicing medicine. It was done over a 3-year period and is a very good report.

Mr. NATCHER. Dr. Shannon, as I said to you in the beginning and as you well know, I am a new member of this subcommittee. There is a whole lot about NIH and HEW that I don't know. All down through the years we have relied on the members of this subcommittee in the Congress as to the presentation of this bill as to amounts, as to conclusions, and as to need. That is the reason I have discussed this matter with you very frankly at this time. I am a little concerned about it, Dr. Shannon.

Mr. Shriver.

Mr. SHRIVER. I have one question. In the book called "The Liberal Arts College and the Emerging Caste System," the author, Earl J. Betts, points out that in the top 10 institutions of higher learning get nearly 40 percent of the Federal research and development funds and the top 100 colleges get 90 percent of the available money. These funds come from the general taxpayer and the general public. My question is, shouldn't these funds be distributed on a wider basis to assist more colleges over the country in this very important element of research.

I assume probably the figures here are similar for the amounts going to universities and medical centers.

Dr. SHANNON. There is less concentration, but there is the same distribution though to a lesser degree.

Mr. Shriver, you ask whether they should be more equitably distributed. My answer to that is no. But I would add that other means should be found to support these educational institutions.

Now, the reason my answer is no is that the bulk of these funds come from mission-oriented agencies that have very serious problems to solve. If they don't search out the best scientific talent, that is available to solve their problems, they are not going to perform their mission.

Now, it so happens that the best scientific talent is concentrated in too few a number of universities. About 25 full-scale universities that, as I said earlier, are first rate.

Our conviction is that this does not adequately reflect the needs of the Nation for full-scale universities that can set a level of achievement in education, technically and technologically, in every region of the Nation. A very positive effort should be made to bring those areas that are devoid of such universities up to the point where they can contribute fully to the scientific and educational life of the Nation.

But I do not think we can divert funds that are granted by Congress to accomplish specific technical missions to the purpose of institutional development.

I think we would be remiss if we turned down a grant applicant at Harvard, which has the highest concentration of any, or perhaps at the University of California, for an applicant in your State, sir, if we were convinced the Harvard man could accomplish the research objective and your man couldn't, simply because we were trying to build up your university. I think we should build up your university, not through the use of mission-oriented funds, but as an end in itself.

Mr. SHRIVER. How else do you subsidize the medical schools than through these research grants?

Dr. SHANNON. There have not been adequate subsidies at the present time, but the new legislative proposal to help the schools will provide adequate subsidies for the medical schools. However, there is a difficulty that should be appreciated. It is a difficulty the Congress has to face up to. The problem is to decide what specialized schools should be included under the Health Professions Educational Assistance Act. Under the present proposals, schools of medicine, dentistry, osteopathy, optometry, and podiatry are included. There is pressure to expand that to include schools of veterinary medicine.

My present view is that we would get the greatest leverage out of

the dollar, at the present time, if these funds are spent in medical schools and schools of osteopathy.

The next greater expenditure should be in the schools of dentistry. The other schools are important to a different degree and they have a different order of magnitude.

What we can do here will be determined by the action of the Congress this spring and summer in dealing with this new legislation. This legislation is aimed directly at providing operational subsidies so that there need be no medical school in this Nation that is not competent. We will retain the excellence we have in our great research centers. It will expand a number of those research centers, but at the same time it will provide, at the very minimum, competence or the wherewithal for competence in all medical schools.

This gets directly at the problem. It faces up to a need and does not try to divert funds which are to accomplish certain scientific missions into an indirect—however badly needed—educational subsidy.

Mr. SHRIVER. I suppose all of us feel within our own States there are certain institutions that are capable of doing research projects. For instance, in my State we have been quite active in mental health for years and years. This has bothered me since I have been in Congress, that on the grant approach that we now have a fair share of the tax dollar is not being distributed to areas of need and where the work can be done.

Dr. SHANNON. To the extent possible geographic distribution is considered in special programs. But in the accomplishment of a specific mission there is nothing short of competence that can be used as the guide.

I might point out that substantial funds from HEW are going into your State. I would be very glad to give you a breakdown.

Mr. SHRIVER. Oh, no, I am just using this as an example because of the statement I just read to you from the book. I have seen other statements like this where most of the research money is being funded.

Dr. SHANNON. When you talk about universities, this figure drops from $15 billion down to about $2 billion. The $15 billion includes development in the broadest sense, such as the development of prototypes by the Department of Defense as, for example, prototype missiles. This is all part of that $15 billion which also includes, this year, I believe $4.5 billion for the space program.

Mr. LAIRD. Part of that is in procurement in the space programs.

Mr. KELLY. Slightly less than $2 billion of the $15 billion is research conducted at colleges and universities or under their administration.

Mr. LAIRD. That is not quite the case if you take in all the contracts.

Dr. SHANNON. Then you get involved in what is a contract laboratory and so forth.

Mr. LAIRD. If you take the contract laboratories at the universities, it is higher than that. If you want to exclude those that we have on the east coast and on the west coast, then you have a different story.

I think you have to consider the contract laboratories too in the universities.

Dr. SHANNON. If you include the Jet Propulsion Laboratory, and the Los Alamos Radiation Laboratory and so forth, it puts the figure substantially higher.

Mr. LAIRD. I never want to disagree with my friend, the Comptroller

of the Department of Health, Education, and Welfare, but that $2 billion figure he is using is direct grants and contracts applied to research on the campuses. It does not include the major overall contract institutions that are under the administration of the various schools of higher education.

Mr. KELLY. It is a recently distributed figure the National Science Foundation put out in a study and I happened to see it the other day.

Dr. Lee also put out a study dealing not with just the research funds, but the total funds of the Department of Health, Education, and Welfare, and how they are distributed to colleges, and universities. While there is still a concentration, when you get into our total funds and you go above research and you get into student loans and the construction of educational facilities and the support of educational programs and training and fellowships, then you find that the distribution of the funds is on a much wider basis, much more nearly related to what the student populations are, and what the population of the country is. But the research funds do carry this concept of competition on the basis of excellence and that there is less than a total geographic spread.

Mr. SHRIVER. I merely wanted your viewpoint. I have it and I thank you.

### CRITERIA FOR FEDERAL GRANTS TO EDUCATIONAL INSTITUTIONS

Mr. SMITH. Dr. Shannon, I think most everybody would agree that research grants and financial aid of that nature should be on the basis of competence, but to some extent aren't we talking about which comes first, the chicken or the egg?

Dr. SHANNON. I would rather you enlarged on that a little bit.

Mr. SMITH. When you give more grants to one that is more competent, they become more competent for subsequent applications while the one at a lower level of competence has more difficulty closing the gap and competing.

Dr. SHANNON. Traditionally we have watched very carefully the growth of biomedical sciences by region and geographic distribution. Indeed, we would be very glad to submit for the record our study of that. We have seen our grant-supported activities move into the South, move into the Midwest, move up into the Northwest. One reason for that is that we do things other than support research. We support training via fellowships, via training grants and the like. Given competence, an individual can leave his environment, acquire his training, and return to it and start a nucleus for research.

The interesting thing is that if one compares the growth of science in the various States with population, per capita income and the State's dedication to education, the growth of the educational apparatuses within the State and the growth of the Federal dollar in that State bears a greater relationship to the State contribution than any other single factor.

Our conviction, from a study of this data, is that a State will develop or not develop depending upon its determination, itself, to make the initial moves.

Mr. SMITH. That helps to prove that if the Federal Government isn't taking initiative in this area, the State must, because the Federal Government's program just helps build up those higher levels of competence.

Dr. SHANNON. I think that is a little distorted version of what I said. Unless the State will provide the resources that can induce an individual to return to a developing academic institution, the State will not develop. It is right to say that the Federal Government, itself, cannot do the whole job, but it can be a very effective partner for any State that has a desire to develop its resources. There are mechanisms by which this can be accomplished and these have been shown in State after State to have operated very effectively. But the Federal Government cannot and, in my belief, should not——

Mr. SMITH. Now, the new program to help raise the level of competence of certain institutions is going to help to increase the competence of the most competent institutions; isn't it?

Dr. SHANNON. No, sir. The most competent institutions are excluded from even consideration.

Mr. SMITH. Well, you have some of a very high level of competence, such as Cornell?

Dr. SHANNON. It is questionable whether Cornell should be so considered. We did not. The situation at Cornell was that they wanted to combine biology activities in the entire university at Ithaca into a single organization—a new division of biological sciencies—to provide, for the first time, competent biology in what, otherwise, was a good university but which, up until that time, had three separate and rather weak biology programs.

### FEDERAL SUPPORT OF MEDICAL EDUCATION

Mr. SMITH. The whole conversation this morning has indicated that research and other Government funds are very important to the maintenance of medical schools which educate medical personnel.

Dr. SHANNON. Indeed, they are, Mr. Smith.

Mr. SMITH. What percentage, on an average, of the total budgets of the financial resources available to medical schools come from Government funds?

Dr. SHANNON. In some it is in excess of 50 percent. I can give you a breakdown, but I can't give you an average figure.

Mr. SMITH. Isn't 50 percent just about the bottom?

Dr. SHANNON. No, sir. Many medical schools get as little as $150,000 or $200,000.

Mr. SMITH. Of course, you must not be counting student loans.

Dr. SHANNON. Oh, no. I am just talking about programs for which we have responsibility.

Mr. SMITH. I mean the total Government support financially through student help and everything else, including research grants.

Dr. SHANNON. The dominant figure, the large money would be contained in our programs, Mr. Smith. What I would be very glad to do would be to make a submission for the record of some schools, taking the top, the middle, and the bottom. I don't know what the figure would be if you added in fellowships, loans, and other things.

Mr. SMITH. I understood one school to say it is something like 52 or 53 percent. They thought that probably the average was considerably above that when one adds fellowships and everything in for total Government support.

Dr. SHANNON. I haven't figures on total Government support, I have figures on our own programs.

Mr. SMITH. My point is, it can make a considerable difference to a school as to whether or not they receive research grants, and also one of our major problems is finding personnel to deliver these medical services. Whether you think that is more important, or the most important problem or not, many agree that is one of the very important problems we have. What I am wondering is, to what extent, if any, has there been an attempt to channel research funds where, there are fairly equal applicants for research funds, to those institutions that are really increasing the personnel output? Is there any consideration given to this at all?

Dr. SHANNON. The study sections give thought to the general needs of institutions and many things go into their judgment, but I cannot assure you this factor plays a significant part.

The Councils very definitely have a bias, given two equal applications, for awarding seed money over just adding another grant to an institution but this does not come up a sufficient number of times for us to be able to document it and say, "This is our policy and here is how it is operated."

I know this to be true on a case-by-case basis, as I have sat in Councils, but I can't tell you how often it happens.

Mr. SMITH. Do you think the Council members are pretty well aware which institutions are trying to increase the output of competent medical personnel?

Dr. SHANNON. I think our staff is; but I am sure the Council isn't.

Mr. SMITH. If the Council isn't aware of that, and isn't thinking about that, how are you going to get any consideration for——

Dr. SHANNON. If there are ancillary factors to consider in making a grant or not making a grant, it is our job to so inform the Council.

Mr. LAIRD. I have gone out and audited Council meetings and have looked over these grants over the period of the last few years. I went just to understand how they work. I have noticed that in most of of the grant applications one of the points they try to make and are making in an increasing way is the effect upon manpower. I think whether the Council knows it or not, this is one of the things that is used as a selling device for many of these grants, the effect it has on manpower, particularly in the last 2 or 3 years.

Mr. SMITH. You would think then that they should be able to train more people.

Mr. LAIRD. I think so.

Dr. SHANNON. That is one of the considerations, but that is done at the study section level and the staff level rather than the Council level, but it is a fact that is cranked into the recommendations of the staff.

Mr. SMITH. There are some institutions that really don't want to get with it and increase the number of personnel like others, isn't that right?

Mr. KELLY. Up until 2 years ago, Mr. Smith, the only money that was available to assist a medical school was through the research and the training and the fellowship area.

Since the enactment of the Health Professions Act, there is a movement that is trying to equate the educational side of medical schools

with the research side, and this is oriented very heavily toward output. The funds are designed to either create new medical schools or to increase the capacity of existing ones.

As a matter of fact, the bias is so great in this direction that in the new bill we are bringing up, we are asking the Congress to identify the fact that a school that is in financial difficulty can't be allowed to go by the boards because it is unable to continue operations while we skew all of the funds for increased production, but, nevertheless, the present law is to pay a premium to the school that is endeavoring to increase the output of health professional manpower.

Mr. SMITH. Is there an attempt to coordinate that same objective in the general research area?

Mr. KELLY. No; because this is the training and development of manpower and the Congress has put the funds up for that purpose rather than being the objective of finding the answer to problems and having it directed to the areas of greatest competence.

Mr. SMITH. The point I am trying to make here is that they are not entirely isolated, that they are not two distinct and separate areas.

Dr. SHANNON. No, sir. This is why our recommendation was accepted by the Secretary when he was considering reorganization. It was that these were so closely interrelated they would greatly profit from administration at a single point, where the various authorities aimed at the production of physicians, on the one hand, and at enhancing science education and research, on the other, might be melded into a single institutional development program. This is what Mr. Gardner had under consideration.

Mr. SMITH. To save institutions that are in danger of going under, would apparently require such an expenditure of money that their percentage of financial support that comes from the Governmen' would be at a very high level; would it not?

Dr. SHANNON. Yes, sir. I cannot tell you what that level would be because I would rather not identify medical schools. If I can go off the record——

RATIO OF PHYSICIANS TO POPULATION

Mr. SMITH. All right.

(Discussion off the record.)

Mr. SMITH. On the record.

We have been told that if all of the anticipated increases in existing medical schools take place, and all the new ones that are anticipated at this time were built and staffed, by 1975 we will have fewer physicians per 100,000 of population than we now have.

It seems to me that to some extent what you have told us indicates that we are not going to reverse this assumption based upon any appropriation that comes before this committee. In other words, we are appropriating more money for facilities and more money for the various things that you ask for here and it is not going to reverse that.

Dr. SHANNON. I would rather Dr. Stewart comment in reference to that. My understanding is that there would be about the same ratio of physicians in 1975 as now.

I would point out that the critical piece of legislation that is aimed directly at this problem is the Health Professions Educational Assist-

ance Act and its revision that will be before the Congress this spring rather than these current appropriations.

Dr. STEWART. Dr. Shannon is quite right. If we realize our goals now, feasible goals, the ratio should stay about the same as physicians to population. The ratio is not a very meaningful figure, though, because one physician is not like another physician. They break into different categories. They distribute themselves differently and they have different levels of proficiency among themselves. It will help to even the ratio if we can continue to get 1600 foreign-trained physicians a year.

Mr. SMITH. What we are hoping for is that the shortage won't be more acute if we secure enough foreign-trained physicians?

Dr. STEWART. The goals that we have at the present time, to maintain the ratio of 20 to 25 schools that we are talking about require the continued licensing of about 1,600 foreign-trained physicians a year. If that were to disappear, it would take about 14, 15 more medical schools.

Mr. KELLY. There are some other areas that do come before you that relate to the same problem. The institute dealing with the improved health systems that Dr. Stewart talked about.

Mr. LAIRD. If you can find better ways to utilize professional manpower, if you can provide better trained paramedical assistance, and if you can develop better methods for the delivery of health services, these physicians will be in a position to render more health services. There is a very considerable amount of appropriations recommended to this committee that is directed at this effort.

Dr. STEWART. That is quite right. We have been stating for some time now that our efforts to increase numbers are to maintain a pool, but this won't solve the problem of shortages. There has to be a proficiency increase of the professionals far beyond what is now existing, by training different kinds of people, by technicians working as a team.

Mr. SMITH. We are so short of personnel and there are so many people that are not getting adequate medical care. When you put all this together, it offers a bleak outlook for the greatest country in the world with an $800 billion a year gross national product. Here we cannot look 8 years ahead and hope to relieve this acute shortage unless we have all of these foreign-trained doctors. As a matter of fact, I think one of the greatest things we could possibly do for foreign relations is to have some doctors that we could send to some other countries. This would provide a great boost in our foreign relations and probably the cheapest way to obtain what we seek in foreign affairs. Here we have got to depend on other countries for part of our manpower.

It seems to me it is absolutely necessary that the bulk of the resources that we are providing by these appropriations be somehow more closely coordinated to the output of doctors. It really is not being done, is it?

Dr. SHANNON. It is not directly being done now, sir. I do not believe that it can be until these programs are coordinated and they have a single administration with clear authority to use funds for such a purpose.

Mr. SMITH. Just how would this be done? Is there something in the mill that would result in this?

Dr. SHANNON. I do not know whether it is in the mill. Acting Secretary Cohen has been asked by the President to come up in some 60 to 90 days with some type of organization proposal for the health function of the executive branch that will provide the most effective and most economical discharge of that function.

Mr. SMITH. You contemplate that pursuant to this approach there might be closer coordination?

Dr. SHANNON. Yes, sir; I think that given all of the things available—institutional development, research into the delivery function itself, the development of ancillary personnel to make better use of the physician—this should not be underrated.

Professor Wedgewood, professor of pediatrics at Washington University, in a study performed some 3 or 4 years ago, came to the conclusion that some 90 percent of what a pediatrician did makes less than full use of his professional capabilities. This points up the need to spread the capabilities of one pediatrician, with a number of assistants, over substantially larger numbers of people. There are studies that are actually experimental programs going on at the present time, trying to seek ways of making broader use of the professional capability of physicians so that a single individual can be utilized at his highest professional competence and consequently reach a larger number of people.

Furthermore, there are areas with a high concentration of physicians in this country, far beyond the absolute needs of the people. There are other areas, particularly the rural areas or the urban ghettos, where the proportion of physicians to those that need care are fantastically low. I think that the President's Manpower Commission pointed out that a redistribution of physicians is one of the mandatory things that has to take place. Incentives should be provided to facilitate such redistribution.

We have three problems: (1) A need for more physicians; (2) broader use of the professional talents; and (3) devices to effect some type of redistribution of services.

As Dr. Stewart or Mr. Kelly said, these things when brought into being will have a very profound effect on the health services delivery system. We have to resolve how this mix can be put together in a more effective manner to solve the problem. I don't feel as hopeless about this as you do.

Mr. SMITH. Are most of these 1,800 foreign-trained physicians coming in per year as well trained as the ones that are trained in the United States?

Dr. SHANNON. Mr. Smith, that is an argument that is raging at the present time. All that I can say is that from my personal experience I cannot make a judgment. The judgment of many people in the medical schools is that they are not. This judgment is based on passing scores on examinations but the physicians who are imported themselves point out that frequently they take their examinations a substantial period of time after they have finished medical school, whereas our students take them immediately after medical school.

The examinations contain a great deal in the way of basic science, physiology, and chemistry, and are in another language from that in which the foreign physician studied. So he has several handicaps and his score—and this is the only thing one has—does not really reflect

his professional capability. I have not worked with them so I am not in a position to make a judgment.

Mr. SMITH. This gets around to the idea that is expressed so much now that we are requiring that all of our personnel be highly trained, highly competent, while we could certainly increase the number of personnel available if we were satisfied with some of them not being quite so highly trained.

If we permit foreign trained doctors to practice who are not as well trained as our U.S. graduates, why shouldn't we lower our requirements to that level?

Dr. SHANNON. I cannot personnally make the judgment they are not. I just point out the statements that have been made by others.

Mr. SMITH. I think that is all.

Mr. NATCHER. Thank you, gentlemen.

I see that you have updated certain statisical data and narrative data that the committee has included each year, for many years, in the hearings record. This will be included at this point.

The committee will adjourn until 2 o'clock Monday.

(The material referred to follows:)

Department of Health, Education, and Welfare
Public Health Service

National Support for Performance of Medical and Health-Related Research
by Source of Funds, Fiscal Years, 1962-1968 1/
(millions of dollars)

| Source of funds | 1962 | 1963 | 1964 | 1965 | 1966 | 1967 | 1968 2/ |
|---|---|---|---|---|---|---|---|
| | Actual | | | | | Estimate | |
| Total | $1,290 | $1,486 | $1,652 | $1,841 | $2,056 | $2,280 | $2,490 |
| Government | 819 | 964 | 1,099 | 1,229 | 1,377 | 1,523 | 1,670 |
| Federal | 782 | 919 | 1,049 | 1,174 | 1,316 | 1,458 | 1,601 |
| State and local | 37 | 45 | 50 | 55 | 61 | 65 | 69 |
| Industry | 336 | 375 | 400 | 450 | 510 | 580 | 640 |
| Private support | 135 | 147 | 153 | 162 | 169 | 177 | 180 |
| Foundations and health agencies | 78 | 85 | 88 | 92 | 94 | 100 | 101 |
| Other private contributions | 18 | 21 | 22 | 25 | 28 | 29 | 30 |
| Endowment | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| Institutions' own funds | 20 | 22 | 24 | 26 | 28 | 29 | 30 |

Note: The Nation's support--from all sources for the conduct of medical research--increased at an average annual rate of 12 percent from 1962 to 1967; the 1968 estimates, however, show a rate of increase of 9 percent over 1967. For agencies of the Federal Government, providing 65 percent of the total funds, 1968 budget estimates indicate an increase in medical research funds of less than 10 percent over 1967, in contrast with the more than 13 percent annual increase in Federal support, 1962-67.

The estimates for medical and health-related research shown above update the series extending back to 1947 published in Resources for Medical Research, Report No. 10, "Dollars for Medical Research, Sources and Performers, 1947-1966," (PHS Publication No. 1612).

Current data for the Federal Government were obtained through the annual survey, conducted by the National Institutes of Health, of Federal agencies' support for medical and health-related research. Estimates for state and local governments include appropriations made to educational institutions and hospitals for the performance of medical and health-related research. The industry sector includes data for the pharmaceutical, medical supply, and biomedical engineering industries. The non-industrial private sector covers the funds provided by philanthropic foundations, voluntary health agencies, and other private contributors to the support of medical and health-related research. Resources for Medical Research Report No. 10 also presents a detailed discussion of the definitions and statistical methodology underlying the time series.

1/ Coverage is limited to conduct and support of medical and health-related research. Support of other activities such as research training or capital outlays for research facilities is not included in this series.

2/ Data on Federal obligations are available at the beginning of the fiscal year. Firm data on non-Federal support cannot be obtained until after the end of the fiscal year; the estimates for 1968 may therefore overstate the Federal share.

Resources Analysis Branch
Office of Program Planning and Evaluation, NIH
February 1968

Department of Health, Education, and Welfare
Public Health Service

Federal Support for Performance of Medical and Health-Related Research, FY 1965-1968 [1]
(thousands of dollars)

| Agency | 1965 Actual | | | 1966 Actual | | | 1967 Actual | | | 1968 Estimate | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Budgeted | Directly related | Total | Budgeted | Directly related | Total | Budgeted | Directly related | Total | Budgeted | Directly related |
| Total | $1,174,208 | $927,625 | $246,583 | $1,316,169 | $1,052,162 | $264,007 | $1,457,952 | $1,179,442 | $278,510 | $1,600,689 | $1,293,188 | $307,501 |
| Atomic Energy Commission | 84,585 | 7,827 | 76,758 | 89,588 | 8,017 | 81,571 | 95,907 | 9,027 | 86,880 | 96,938 | 9,897 | 87,041 |
| National Aeronautics and Space Administration | 60,000 | -- | 60,000 | 75,352 | -- | 75,352 | 81,623 | -- | 81,623 | 108,185 | -- | 108,185 |
| National Science Foundation | 19,678 | -- | 19,678 | 13,812 | -- | 13,812 | 13,845 | -- | 13,845 | 13,055 | -- | 13,055 |
| Tennessee Valley Authority | 534 | -- | 534 | 945 | -- | 945 | 1,484 | -- | 1,484 | 2,107 | -- | 2,107 |
| Veteran's Administration | 36,907 | 36,907 | -- | 40,673 | 40,673 | -- | 44,754 | 44,754 | -- | 46,461 | 46,461 | -- |
| Department of Agriculture | 40,470 | -- | 40,470 | 44,661 | -- | 44,661 | 45,440 | -- | 45,440 | 45,734 | -- | 45,734 |
| Department of Commerce | 366 | 33 | 333 | 772 | -- | 772 | 1,059 | -- | 1,059 | 1,038 | -- | 1,038 |
| Department of Defense | 101,261 | 53,461 | 47,800 | 119,153 | 75,617 | 43,536 | 117,322 | 73,165 | 44,157 | 113,347 | 70,566 | 42,781 |
| Department of Health, Education and Welfare | 826,200 | 825,828 | 372 | 925,259 | 923,843 | 1,416 | 1,049,946 | 1,047,900 | 2,046 | 1,166,374 | 1,160,784 | 5,590 |
| Public Health Service | (781,849) | (781,849) | -- | (879,230) | (879,230) | -- | (1,001,275) | (1,001,275) | -- | (1,110,110) | (1,110,110) | -- |
| NIH [2] | (715,072) | (715,072) | -- | (790,927) | (790,927) | -- | (802,830) | (802,830) | -- | (873,230) | (873,230) | -- |
| NIMH [2] | -- | -- | -- | -- | -- | -- | (100,985) | (100,985) | -- | (114,244) | (114,244) | -- |
| Other PHS | (66,777) | (66,777) | -- | (88,303) | (88,303) | -- | (97,460) | (97,460) | -- | (122,636) | (122,636) | -- |
| Other DHEW | (44,351) | (43,979) | (372) | (46,029) | (44,613) | (1,416) | (48,671) | (46,625) | (2,046 | (56,264) | (50,674) | (5,590) |
| Department of Interior | 618 | -- | 618 | 1,942 | -- | 1,942 | 1,976 | -- | 1,976 | 1,970 | -- | 1,970 |
| Department of State | 771 | 771 | -- | 1,516 | 1,516 | -- | 2,166 | 2,166 | -- | 2,400 | 2,400 | -- |
| Department of Transportation [3] | 2,798 | 2,798 | -- | 2,496 | 2,496 | -- | 2,430 | 2,430 | -- | 3,080 | 3,080 | -- |

For 1968, the current fiscal year, a less than 10 percent increase over 1967 is projected in Federal funds for medical research performed in Federal and nonfederal laboratories and clinics. This estimated annual increase is the smallest since 1947, with the exception of the 1952-53 period affected by the budgetary constraints imposed by the Korean war. This increase, however, is not uniform among the twelve Federal agencies with medical research programs. Reflecting particular National objectives, the medical research programs, for instance, of the National Aeronautics and Space Administration are projected to increase 30 percent for an expanded program in aerospace medicine and in the life sciences in support of manned space flights; and the research programs of the Public Health Service for air pollution and environmental control are projected to increase more than 25 percent.

Note on Coverage and Sources

The statistics shown above -- actual obligations for fiscal years 1965, 1966, 1967 and estimates for 1968 -- were reported by Federal agencies to NIH following a review by each agency of its research activities to show explicitly obligations for medical and health-related in all fields of science (biological, medical, agricultural, psychological, physical, mathematical, engineering, social) distinguishing between (1) funds separately budgeted for medical and health-related research, specifically identified, programmed and justified as such, and supported for the purpose of improving human health (all the research activities of agencies or sub-agencies whose sole mission is advancement of human health through research may thus be included); and (2) funds for research directly related to health in terms of substance or probable application, but which derive from funds budgeted, justified or supported for purposes other than medical or health objectives (for example, the general support of science, the promotion of agriculture, the achievement of the Nation's strategic objectives in outer space.) As the table shows, about 20% of the total represents this latter category of research directly related to health but supported for other purposes. The above up-date and continue the time series presented in Resources for Medical Research "Federal Support for Medical and Health-Related Research, 1947-1964," Report No. 4. (PHS publication No. 1068) and Resources for Medical Research Report No. 10, "Dollars for Medical Research, Sources and Performers 1947-1966" (PHS publication No. 1612). These publications together with the revised data shown above for 1965-67 constitute the definitive time series od Federal support for the performance of medical and health-related research in the post-war period.

1/ Coverage is limited to conduct and support of medical and health-related research. Support of other activities (such as training or capital outlays for research facilities) is not now included in this series.
2/ Effective January 1, 1967, the National Institutes of Mental Health became a separate Bureau of the Public Health Service; prior to that time it was one of the Institutes in the National Institutes of Health. On the same date the National Environmental Health Sciences Center in North Carolina, and the related extramural program of support for research in the environmental health sciences was transferred to NIH from the Bureau of State Services -- Public Health Service. Data for 1967 and 1968 reflect these transfers.
3/ Represents programs of the Federal Aviation Administration.

Resources Analysis Branch
Office of Program Planning and Evaluation, NIH
February 1968

HISTORY OF CONGRESSIONAL ACTION ON BUDGET REQUESTS FOR NIH

| Year | Budget request | | | Appropriation | | |
|---|---|---|---|---|---|---|
| | Obligational cash | Liquidating cash | Contract authority | Obligational cash | Liquidating cash | Contract authority |
| 1932 | $48,000 | ---------- | ---------- | $48,000 | ---------- | ---------- |
| 1933 | 48,000 | ---------- | ---------- | 48,000 | ---------- | ---------- |
| 1934 | 54,775 | ---------- | ---------- | 54,775 | ---------- | ---------- |
| 1935 | 50,000 | ---------- | ---------- | 50,000 | ---------- | ---------- |
| 1936 | 64,000 | ---------- | ---------- | 64,000 | ---------- | ---------- |
| 1937 | 64,000 | ---------- | ---------- | 64,000 | ---------- | ---------- |
| 1938 | 464,000 | ---------- | ---------- | 464,000 | ---------- | ---------- |
| 1939 | 515,000 | ---------- | ---------- | 515,000 | ---------- | ---------- |
| 1940 | 587,750 | ---------- | ---------- | 707,000 | ---------- | ---------- |
| 1941 | 712,120 | ---------- | ---------- | 711,000 | ---------- | ---------- |
| 1942 | 705,000 | ---------- | ---------- | 700,000 | ---------- | ---------- |
| 1943 | 1,278,270 | ---------- | ---------- | 1,278,270 | ---------- | ---------- |
| 1944 | 1,291,000 | ---------- | ---------- | 2,555,020 | ---------- | ---------- |
| 1945 | 2,835,000 | ---------- | ---------- | 2,835,000 | ---------- | ---------- |
| 1946 | 2,078,000 | ---------- | ---------- | 3,414,700 | ---------- | ---------- |
| 1947 | 10,799,500 | ---------- | ---------- | 8,125,448 1/ | ---------- | ---------- |
| 1948 | 22,403,000 | ---------- | ---------- | 28,876,000 | ---------- | ---------- |
| 1949 | 45,701,460 | ---------- | $2,300,000 | 37,668,000 | ---------- | $10,300,000 |
| 1950 | 40,567,000 | $3,900,000 | 3,595,000 | 50,167,000 2/ | $4,925,000 2/ | 15,425,000 |
| 1951 | 49,845,000 | 12,725,000 | ---------- | 47,334,750 3/ | 12,725,000 | ---------- |
| 1952 | 53,386,000 | 5,648,000 | ---------- | 52,477,291 | 5,198,000 | ---------- |
| 1953 | 55,005,000 | ---------- | ---------- | 59,030,750 | ---------- | ---------- |
| 1954 | 56,340,000 | ---------- | ---------- | 71,153,000 | ---------- | ---------- |
| 1955 4/ | 71,128,000 | ---------- | ---------- | 81,268,000 | ---------- | ---------- |
| 1956 5/ 6/ | 90,023,000 | ---------- | ---------- | 98,458,000 | ---------- | ---------- |
| 1957 7/ | 126,725,000 7/ | ---------- | ---------- | 183,007,000 | ---------- | ---------- |
| 1958 | 190,183,000 | ---------- | ---------- | 211,183,000 | ---------- | ---------- |
| 1959 | 211,814,000 | ---------- | ---------- | 294,383,000 | ---------- | ---------- |
| 1960 | 294,279,000 | ---------- | ---------- | 400,000,000 | ---------- | ---------- |
| 1961 | 400,000,000 | ---------- | ---------- | 560,000,000 8/ | ---------- | ---------- |
| 1962 | 583,000,000 | ---------- | ---------- | 738,335,000 9/ | ---------- | ---------- |
| 1963 | 780,400,000 | ---------- | ---------- | 880,800,000 | ---------- | ---------- |
| 1964 | 930,454,000 | ---------- | ---------- | 918,454,000 | ---------- | ---------- |
| 1965 | 956,492,000 | ---------- | ---------- | 965,992,000 | ---------- | ---------- |
| 1966 10/ | 1,105,006,000 | ---------- | ---------- | 1,138,406,000 | ---------- | ---------- |
| 1967 11/ | 1,231,764,000 | ---------- | ---------- | 1,306,283,000 12/ | ---------- | ---------- |
| 1968 11/ | 1,152,290,000 | ---------- | ---------- | 1,243,424,000 13/ | ---------- | ---------- |
| 1969 | 1,188,293,000 11/ | ---------- | ---------- | ---------- | ---------- | ---------- |

1/ Includes $386,500 transfers.
2/ Not less than $3,000,000 was earmarked for liquidating cash; an additional $1,175,000 was used for that purpose.
3/ Excludes $3,216,250 rescinded.
4/ Excludes $131,000 for Gorgas Memorial Laboratory.
5/ Excludes $147,000 for Gorgas Memorial Laboratory.
6/ Includes $90,000 transfer.
7/ Includes $200,000 transfer from other appropriations.
8/ Includes $12,139,000 for construction of mental health-neurology research facility.
9/ Includes $1,000,000 for planning for a gerontological research facility; and $750,000 for modernization at the Rocky Mountain Laboratory, Hamilton, Montana.
10/ Includes $25,000,000 for Regional Medical Programs, $19,700,000 for Mental Health Staffing, and $20,250,000 for Heart Disease, Cancer and Stroke Program.
11/ Excludes $246,741,000 for National Institute of Mental Health. Includes $20,615,000 for Environmental Health Sciences. Excludes $21,000,000 unobligated balance available, start of year, for Regional Medical Programs.
12/ Excludes $21,000,000 unobligated balance available, start of year, for Regional Medical Programs.
13/ Excludes $30,900,000 unobligated balance available, start of year, for Regional Medical Programs.

NOTE:--Not all amounts in this table are comparable from year to year because of inconsistencies in the content of the appropriations. Prior to 1938 they exclude all salaries. Prior to 1943 they exclude all salaries other than those of employees of the National Cancer Institute. Prior to 1949 they exclude pay of regular corps officers. For 1948, 1949, and 1950 they include funds for support of narcotic hospitals at Fort Worth and Lexington which were subsequently transferred.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

SUMMARY--NATIONAL INSTITUTES OF HEALTH

| Total, operating accounts: | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $189,706,000[1] | $175,036,000 | $174,026,000 | $178,986,000 | $264,681,000 | $241,964,000 | $235,426,000 |
| 1960---- | 278,848,000 | 255,130,000 | 241,895,000 | 283,870,000 | 400,618,000 | 331,910,000 | 322,807,000 |
| 1961---- | 368,139,600 | 336,463,600 | 332,437,000 | 375,137,000 | 553,200,000 | 459,100,000 | 448,425,000[2] |
| 1962---- | 570,875,000 | 548,818,000 | 494,676,000 | 548,818,000 | 710,100,000 | 629,459,000 | 530,441,000 |
| 1963---- | 746,662,000 | 719,200,000 | 653,501,000 | 707,201,000 | 752,201,000 | 737,201,000 | 612,156,000 |
| 1964---- | 853,673,000 | 764,759,000[3] | 742,333,000 | 736,326,000 | 741,518,000 | 736,326,000 | 710,187,000 |
| 1965---- | 861,055,000[3] | 832,277,000[3] | 778,327,000 | 773,349,000 | 787,949,000 | 787,099,000 | 781,670,000 |
| 1966---- | 987,295,000 | 932,905,000 | 892,270,000 | 878,970,000 | 927,320,000 | 921,720,000 | 910,325,000 |
| 1967---- | 1,185,720,000 | 1,137,245,000 | 1,002,961,000 | 1,037,162,000 | 1,072,162,000 | 1,067,162,000 | 1,021,162,000 |
| 1968---- | 1,402,955,000 | 1,309,111,000 | 1,152,250,000 | 1,138,924,000 | 1,201,500,000 | 1,143,424,000 | ---------- |
| 1969[4]-- | 1,330,562,185 | 1,302,978,185 | 1,188,293,000 | ---------- | ---------- | ---------- | ---------- |

1 Subsequent to 1958 Senate allowance this amount was increased to $195,253,000.

2 Includes $7,000,000 transferred to "Construction of Mental Health-Neurology Research Facility".

3 Includes $30,000,000 for "Special Cancer Research".

4 Includes $600,000 direct operating funds for the International Center.

NOTE:--

Excludes the "National Institutes of Mental Health" established as a bureau in 1967.

Includes the "Division of Environmental Health Sciences" established as a part of "NIH" in 1967.

"Obligations", on all tables, include rental payments made to GSA by transfer.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

BIOLOGICS STANDARDS

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1964---- | $4,868,000 | $4,868,000 | $4,817,000 | $4,787,000 | $4,787,000 | $4,787,000 | $4,273,000 |
| 1965---- | 5,075,000 | 5,075,000 | 4,969,000 | 4,969,000 | 4,969,000 | 4,969,000 | 4,433,000 |
| 1966---- | 7,894,000 | 7,864,000 | 6,406,000 | 6,406,000 | 7,206,000 | 6,806,000 | 5,256,000 |
| 1967---- | 8,597,000 | 8,524,000 | 7,905,000 | 7,904,000 | 7,904,000 | 7,904,000 | 6,979,000 |
| 1968---- | 9,280,000 | 9,280,000 | 8,649,000 | 8,649,000 | 8,649,000 | 8,649,000 | ---------- |
| 1969---- | 8,942,760 | 8,910,760 | 8,499,000 | ---------- | ---------- | ---------- | ---------- |

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL CANCER INSTITUTE

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $58,943,000 | $56,744,000 | $56,060,000 | $57,423,000 | $81,129,000 | $75,268,000 | $69,398,000 |
| 1960---- | 81,864,000 | 80,232,000 | 75,218,000 | 83,308,000 | 110,203,000 | 91,257,000 | 85,030,000 |
| 1961---- | 95,995,400 | 88,785,400 | 88,869,000 | 102,469,000 | 126,375,000 | 111,000,000 | 106,262,000 |
| 1962---- | 129,519,000 | 125,672,000 | 117,167,000 | 125,672,000 | 160,000,000 | 142,836,000 | 110,352,000 |
| 1963---- | 158,901,000 | 155,700,000 | 139,109,000 | 150,409,000 | 158,409,000 | 155,742,000 | 122,424,000 |
| 1964---- | 154,999,000 | 145,706,000 | 145,114,000 | 144,340,000 | 145,114,000 | 144,340,000 | 131,349,000 |
| 1965---- | 147,504,000 | 145,664,000 | 139,714,000 | 138,970,000 | 138,970,000 | 138,970,000 | 139,041,000 |
| 1966[1]-- | 170,974,000 | 160,950,000 | 153,968,000 | 157,618,000 | 163,768,000 | 163,768,000 | 161,374,000 |
| 1967---- | 188,134,000 | 176,594,000 | 163,957,000 | 170,656,000 | 175,656,000 | 175,656,000 | 173,283,000 |
| 1968---- | 198,580,000 | 193,058,000 | 183,356,000 | 183,356,000 | 192,356,000 | 183,356,000 | ---------- |
| 1969---- | 207,348,030 | 201,413,030 | 187,707,000 | ---------- | ---------- | ---------- | ---------- |

1 Includes $10,000,000 transferred from "Special Cancer Research" appropriation in 1966.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

SPECIAL CANCER RESEARCH

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropria-tion | Obligations |
|---|---|---|---|---|---|---|---|
| 1965---- | $30,000,000 | $30,000,000 | ---------- | ---------- | $10,000,000 | $10,000,000 | $10,000,000 |

NOTE:--Transferred to "National Cancer Institute" appropriation in 1966.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL HEART INSTITUTE

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $34,683,000[1/] | $34,924,000 | $34,820,000 | $36,212,000 | $49,529,000 | $45,613,000 | $45,468,000 |
| 1960---- | 52,911,000 | 47,671,000 | 45,594,000 | 52,744,000 | 89,500,000 | 62,237,000 | 61,565,000 |
| 1961---- | 69,798,700 | 65,047,700 | 63,162,000 | 71,762,000 | 125,166,000 | 86,900,000 | 86,239,000 |
| 1962---- | 110,205,000 | 105,723,000 | 97,073,000 | 105,723,000 | 160,100,000 | 132,912,000 | 91,053,000 |
| 1963---- | 155,712,000 | 148,000,000 | 126,898,000 | 143,398,000 | 149,398,000 | 147,398,000 | 104,343,000 |
| 1964---- | 148,884,000 | 132,784,000 | 130,108,000 | 129,325,000 | 130,545,000 | 129,325,000 | 117,405,000 |
| 1965---- | 132,489,000 | 129,156,000 | 125,640,000 | 124,521,000 | 125,171,000 | 125,171,000 | 124,061,000 |
| 1966---- | 146,821,000 | 146,575,000 | 141,412,000 | 146,212,000 | 143,462,000 | 141,462,000 | 141,167,000 |
| 1967---- | 171,226,000 | 172,766,000 | 148,407,000 | 154,770,000 | 169,770,000 | 164,770,000 | 164,333,000 |
| 1968---- | 194,796,000 | 190,385,000 | 167,954,000 | 167,954,000 | 177,954,000 | 167,954,000 | ---------- |
| 1969---- | 190,515,000 | 189,148,000 | 169,735,000 | ---------- | ---------- | ---------- | ---------- |

[1] Subsequent to 1958 Senate allowance this amount was increased to $37,139,000.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF DENTAL RESEARCH

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $7,719,000 | $6,481,000 | $6,359,000 | $6,543,000 | $7,923,000 | $7,420,000 | $7,405,000 |
| 1960---- | 9,907,000 | 7,715,000 | 7,420,000 | 9,725,000 | 10,164,000 | 10,019,000 | 9,968,000 |
| 1961---- | 13,803,300 | 11,996,300 | 11,204,000 | 12,604,000 | 16,710,000 | 15,500,000 | 14,616,000 |
| 1962---- | 15,265,000 | 14,681,000 | 13,933,000 | 14,681,000 | 20,000,000 | 17,340,000 | 12,963,000 |
| 1963---- | 20,017,000 | 19,700,000 | 17,199,000 | 19,199,000 | 22,199,000 | 21,199,000 | 17,451,000 |
| 1964---- | 23,314,000 | 20,212,000 | 19,809,000 | 19,689,000 | 19,809,000 | 19,689,000 | 19,151,000 |
| 1965---- | 21,055,000 | 20,402,000 | 20,209,000 | 20,090,000 | 20,190,000 | 20,190,000 | 20,001,000 |
| 1966---- | 22,460,000 | 22,658,000 | 22,177,000 | 22,177,000 | 23,677,000 | 23,677,000 | 23,482,000 |
| 1967---- | 29,600,000 | 26,208,000 | 24,884,000 | 28,308,000 | 28,308,000 | 28,308,000 | 28,067,000 |
| 1968---- | 32,388,000 | 31,926,000 | 30,307,000 | 30,307,000 | 32,307,000 | 30,307,000 | ---------- |
| 1969---- | 34,121,391 | 33,676,391 | 30,414,000 | ---------- | ---------- | ---------- | ---------- |

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $20,319,000[1/] | $20,579,000 | $20,668,000 | $21,092,000 | $34,798,000 | $31,215,000 | $31,126,000 |
| 1960---- | 37,014,000 | 32,564,000 | 31,215,000 | 37,790,000 | 51,200,000 | 46,862,000 | 46,182,000 |
| 1961---- | 52,949,900 | 47,519,900 | 47,541,000 | 52,841,000 | 70,760,000 | 61,200,000 | 58,608,000 |
| 1962---- | 77,783,000 | 73,661,000 | 68,740,000 | 73,661,000 | 90,000,000 | 81,831,000 | 78,559,000 |
| 1963---- | 103,761,000 | 101,560,000 | 91,921,000 | 98,721,000 | 105,721,000 | 103,388,000 | 95,110,000 |
| 1964---- | 124,579,000 | 115,759,000 | 114,717,000 | 113,679,000 | 114,717,000 | 113,679,000 | 104,970,000 |
| 1965---- | 121,908,000 | 117,432,000 | 113,369,000 | 112,344,000 | 113,544,000 | 113,344,000 | 112,592,000 |
| 1966---- | 121,502,000 | 121,818,000 | 119,203,000 | 121,203,000 | 123,203,000 | 123,203,000 | 121,622,000 |
| 1967---- | 142,265,000 | 137,506,000 | 129,908,000 | 133,687,000 | 135,687,000 | 135,687,000 | 133,508,000 |
| 1968---- | 156,889,000 | 153,157,000 | 143,954,000 | 143,954,000 | 147,204,000 | 143,954,000 | ---------- |
| 1969---- | 157,239,000 | 154,089,000 | 146,489,000 | ---------- | ---------- | ---------- | ---------- |

1 Subsequent to 1958 Senate allowance this amount was increased to $21,929,000.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $20,778,000 | $20,871,000 | $20,760,000 | $21,977,000 | $32,250,000 | $29,403,000 | $29,033,000 |
| 1960---- | 32,727,000 | 30,803,000 | 29,403,000 | 33,613,000 | 48,966,000 | 41,487,000 | 40,248,000 |
| 1961---- | 44,404,100 | 40,386,100 | 39,662,000 | 44,362,000 | 61,550,000 | 56,600,000 | 55,348,000[1] |
| 1962---- | 60,587,000 | 57,624,000 | 54,100,000 | 57,624,000 | 80,000,000 | 70,812,000 | 61,208,000 |
| 1963---- | 82,158,000 | 79,785,000 | 71,206,000 | 77,506,000 | 86,506,000 | 83,506,000 | 70,794,000 |
| 1964---- | 95,379,000 | 89,270,000 | 88,407,000 | 87,675,000 | 88,407,000 | 87,675,000 | 81,970,000 |
| 1965---- | 94,532,000 | 91,491,000 | 88,608,000 | 87,889,000 | 88,089,000 | 88,089,000 | 87,751,000 |
| 1966---- | 104,489,000 | 100,294,000 | 96,403,000 | 96,403,000 | 102,153,000 | 101,153,000 | 100,250,000 |
| 1967---- | 118,868,000 | 113,386,000 | 106,418,000 | 111,296,000 | 116,296,000 | 116,296,000 | 113,067,000 |
| 1968---- | 134,540,000 | 134,359,000 | 128,633,000 | 128,633,000 | 135,633,000 | 128,633,000 | ---------- |
| 1969---- | 146,438,726 | 149,019,726 | 131,195,000 | ---------- | ---------- | ---------- | ---------- |

[1] Includes $7,000,000 transferred to "Construction of mental health-neurology research facility".

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $21,044,000 | $17,663,000 | $17,593,000 | $17,997,000 | $26,500,000 | $24,071,000 | $24,039,000 |
| 1960---- | 29,126,000 | 25,379,000 | 24,071,000 | 30,286,000 | 41,000,000 | 34,054,000 | 34,025,000 |
| 1961---- | 38,477,100 | 35,462,100 | 34,739,000 | 38,439,000 | 48,234,000 | 44,000,000 | 43,780,000 |
| 1962---- | 54,833,000 | 52,182,000 | 48,322,000 | 52,182,000 | 60,000,000 | 56,091,000 | 53,303,000 |
| 1963---- | 64,262,000 | 64,155,000 | 59,342,000 | 62,142,000 | 68,142,000 | 66,142,000 | 62,387,000 |
| 1964---- | 79,569,000 | 69,765,000 | 69,226,000 | 68,723,000 | 69,226,000 | 68,723,000 | 66,213,000 |
| 1965---- | 70,995,000 | 69,256,000 | 68,600,000 | 70,100,000 | 70,400,000 | 70,100,000 | 69,742,000 |
| 1966---- | 76,558,000 | 77,003,000 | 74,987,000 | 74,987,000 | 77,987,000 | 77,987,000 | 77,710,000 |
| 1967---- | 98,186,000 | 94,684,000 | 85,702,000 | 88,670,000 | 90,670,000 | 90,670,000 | 89,598,000 |
| 1968---- | 96,668,000 | 96,086,000 | 94,422,000 | 94,422,000 | 98,922,000 | 94,422,000 | ---------- |
| 1969---- | 105,471,598 | 106,653,598 | 98,562,000 | ---------- | ---------- | ---------- | ---------- |

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1966---- | $146,306,000 | $137,753,000 | $124,538,000 | $124,538,000 | $129,388,000 | $127,188,000 | $127,064,000 |
| 1967---- | 155,528,000 | 146,854,000 | 137,175,000 | 142,613,000 | 145,113,000 | 145,113,000 | 144,805,000 |
| 1968---- | 167,113,000 | 163,485,000 | 160,284,000 | 160,284,000 | 164,284,000 | 160,284,000 | ---------- |
| 1969---- | 186,193,000 | 175,481,000 | 165,777,000 | ---------- | ---------- | ---------- | ---------- |

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1964---- | ($34,000,000) | ($34,000,000) | ($34,000,000) | ($34,000,000) | ($34,000,000) | ($34,000,000)[1/] | $30,450,000 |
| 1965---- | 49,147,000 | 44,487,000 | 43,152,000 | 42,696,000 | 42,696,000 | 42,696,000 | 41,320,000 |
| 1966---- | 60,220,000 | 55,860,000 | 53,524,000 | 53,524,000 | 55,024,000 | 55,024,000 | 53,615,000 |
| 1967---- | 68,560,000 | 68,349,000 | 61,448,000 | 61,422,000 | 64,922,000 | 64,922,000 | 62,237,000 |
| 1968---- | 80,292,000 | 76,211,000 | 68,621,000 | 68,621,000 | 74,621,000 | 68,621,000 | ---------- |
| 1969---- | 80,569,100 | 77,975,100 | 75,394,000 | ---------- | ---------- | ---------- | ---------- |

1 Congress authorized the transfer of $34,000,000 from other NIH appropriations to establish the National Institute of Child Health and Human Development.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

REGIONAL MEDICAL PROGRAMS

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1966[1/] -- | $51,000,000 | $25,000,000 | $25,000,000 | ----------[2/] | $25,000,000 | $25,000,000 | $2,553,000 |
| 1967---- | 92,447,000 | 92,024,000 | 45,024,000 | $45,004,000 | 45,004,000 | 45,004,000 | 28,900,000 |
| 1968---- | 202,799,000 | 140,600,000 | 64,314,000 | 54,314,000 | 64,314,000 | 58,814,000 | ---------- |
| 1969---- | 98,683,420 | 91,250,420 | 68,922,000 | | | | |

1 Supplemental appropriation.

2 Not considered by the House.

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1964---- | $10,180,000 | $7,029,000 | $5,461,000 | $4,239,000 | $4,239,000 | $4,239,000 | $4,209,000 |
| 1965---- | 10,993,000 | 10,993,000 | 10,920,000 | 9,380,000 | 9,730,000 | 9,380,000 | 9,227,000 |
| 1966---- | 18,367,000 | 18,049,000 | 15,933,000 | 15,933,000 | 15,983,000 | 15,983,000 | 15,735,000 |
| 1967---- | 32,153,000 | 26,516,000 | 24,312,000 | 24,298,000 | 24,298,000 | 24,298,000 | 11,917,000 |
| 1968---- | 28,059,000 | 21,994,000 | 20,615,000 | 17,289,000 | 20,615,000 | 17,289,000 | ---------- |
| 1969---- | 24,559,666 | 24,319,666 | 18,099,000 | ---------- | ---------- | ---------- | ---------- |

APPROPRIATION HISTORY AND OBLIGATIONS, 1959-69

GENERAL RESEARCH AND SERVICES

| | PHS estimate to Department | Department estimate to Bureau of the Budget | Bureau of the Budget allowance | House allowance | Senate allowance | Appropriation | Obligations |
|---|---|---|---|---|---|---|---|
| 1959---- | $26,220,000 | $17,774,000 | $17,766,000 | $17,742,000 | $32,552,000 | $28,974,000 | $28,957,000 |
| 1960---- | 35,299,000 | 30,766,000 | 28,974,000 | 36,404,000 | 49,585,000 | 45,994,000 | 45,789,000 |
| 1961---- | 52,711,100 | 47,266,100 | 47,260,000 | 52,660,000 | 104,405,000 | 83,900,000 | 83,572,000 |
| 1962---- | 122,683,000 | 119,275,000 | 95,341,000 | 119,275,000 | 140,000,000 | 127,637,000 | 119,966,000 |
| 1963---- | 161,851,000 | 150,300,000 | 147,826,000 | 155,826,000 | 161,826,000 | 159,826,000 | 136,126,000 |
| 1964---- | 211,901,000 | 179,366,000 | 164,674,000 | 163,869,000 | 164,674,000 | 163,869,000 | 150,197,000 |
| 1965[1]-- | 177,357,000 | 168,321,000 | 163,146,000 | 162,390,000 | 164,190,000 | 164,190,000 | 163,502,000 |
| 1966[1]-- | 60,704,000 | 59,081,000 | 58,719,000 | 59,969,000 | 60,469,000 | 60,469,000 | 58,563,000 |
| 1967---- | 80,156,000 | 73,834,000 | 67,821,000 | 68,534,000 | 68,534,000 | 68,534,000 | 64,468,000 |
| 1968---- | 101,551,000 | 98,570,000 | 81,141,000 | 81,141,000 | 84,641,000 | 81,141,000 | ---------- |
| 1969[2]-- | 90,480,494 | 91,041,494 | 87,500,000 | ---------- | ---------- | ---------- | ---------- |

[1] Excludes the "National Institute of General Medical Sciences" established as a separate appropriation in 1966.

[2] Includes $600,000 direct operating funds for the International Center.

DESCRIPTION OF EACH NIH AND NIMH GRANT PROGRAM

NIH

The data presented below include data from the National Institute of Mental Health through 1966, NIMH became a separate Bureau in 1967. The data includes the Division of Environmental Health Sciences beginning with 1967 when it became an NIH component.

REGULAR RESEARCH GRANTS

1. Purpose of program

To provide grant support of research in health, medicine, and allied fields with the major objectives (1) of continuing existing programs of research, (2) of expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions and (3) of stimulating new investigations in fields needing exploration. The grants range from support of smaller, discrete, and circumscribed projects, which are defined as project grants, to support of broad programs which integrate the research interests of several investigators, and which are called program project grants.

2. Funds

| | |
|---|---|
| 1959 obligations | $139,629,000 |
| 1960 obligations | 185,474,000 |
| 1961 obligations | 240,607,000 |
| 1962 obligations | 305,527,000 |
| 1963 obligations | 353,102,000 |
| 1964 obligations | 401,868,000 |
| 1965 obligations | 425,516,000 |
| 1966 obligations | 461,756,000 |
| 1967 obligations | 448,431,000 |
| 1968 estimates | 468,617,000 |
| 1969 estimates | 487,418,000 |

3. Present stage of development

The modest cancer grants program of 1938-1945 of less than $100,000 annually changed in 1946 to a health, medicine, and related sciences program of $780,000. Steady annual increases since 1946 have produced the 1968 program of about $627 million in regular and special research grant programs. This will support about 14,100 research projects conducted in over 1,600 institutions throughout this country and abroad, and covering the full range of biological and related research. While the program continues in major part to support the ideas of investigators in the grantee institutions, a significant part of the grants provide support of programs reflecting initiative of NIH staff, such as cancer chemotherapy and psychopharmacology.

4. Plans for the future

The NIH believes that medical research should continue to expand as long as this country is faced with major crippling and killing diseases and conditions. Further, it believes that a number of factors contribute together to provide full assurance that substantial expansion can be effected. These factors include (1) a sharp expansion in the population base from which new M.D.'s and PH.D's will be drawn, (2) a steadily rising college enrollment, (3) significant percentage increase in graduate enrollment, and (4) improving educational opportunities for the more talented students, including both new medical schools and strengthened graduate and professional schools.

GENERAL RESEARCH SUPPORT GRANTS

1. Purpose of program

To provide funds for the general support of the medical research and research training programs of institutions under conditions enabling the recipients to meet needs which could not be effectively met by other forms of support. The grants can be utilized for such purposes as capitalizing on emerging research opportunities, exploring new and unorthodox ideas, or stimulating and developing an over-all research or research training program. The broad type of support made possible through these grants can enable an institution to achieve a better balance of their total research and training programs, and permit the recipient institutions to strengthen their overall biomedical research capabilities under conditions and in directions of their own choice.

2. Funds

The amount available for distribution to this program constitutes "such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health ..." (Public Law 86-798).

| | |
|---|---|
| 1962 obligations | $20,000,000 |
| 1963 obligations | 30,000,000 |
| 1964 obligations | 35,000,000 |
| 1965 obligations | 45,000,000 |
| 1966 obligations | 45,200,000 |
| 1967 obligations | 1/ 51,700,000 |
| 1968 estimates | 1/ 59,700,000 |
| 1969 estimates | 1/ 60,700,000 |

1/ An amount for NIMH is included here (1967--$6,434,000; 1968--$5,483,000; 1969--$7,755,000) inasmuch as the total is obligated through NIH.

3. Present stage of development

In 1968 general research support grants will provide support for 311 health professional schools, hospitals, research institutes, laboratories, centers and certain other nonprofit research organizations heavily engaged in health related research. In addition approximately 96 academic institutions other than health professional schools will be supported. Approximately nine institutional advancement awards will also be made. These awards are intended to encourage the recipient institutions to enter the health research field for the first time or to expand and improve their present biomedical research activities.

4. Plans for the future

The 1969 President's budget continues this program with an increased level of support, including support for 326 institutions or organizations under the basic program 99 biomedical sciences support grants to academic institutions and 11 Health-Sciences Advancement Awards.

SCIENTIFIC EVALUATION AND PLANNING GRANTS (CHAIRMEN'S GRANTS)

1. Purpose of the program

To provide funds for the assistance of the national Advisory councils through the technical and scientific review of research grant applications, and through the support of meetings used for the exchange of scientific views.

2. Funds

| | |
|---|---|
| 1962 obligations | $1,244,000 |
| 1963 obligations | 1,516,000 |
| 1964 obligations | 1,847,000 |
| 1965 obligations | 2,030,000 |
| 1966 obligations | 2,163,000 |
| 1967 obligations | 2,040,000 |
| 1968 estimates | 2,443,000 |
| 1969 estimates | 2,443,000 |

3. Present stage of development

Research grant applications are reviewed prior to submission to the advisory councils by the appropriate study section. Each of these more than 50 sections has scientific competency in a particular field or research discipline. Each section is comprised of outstanding leaders in the relevant specialities who are usually not employees of the Federal Government.

In addition to financing these review activities, chairman's grants support an extensive group of ad hoc panels, symposia, converences, and other types of meetings used for the exchange of professional views.

## INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

1. Purpose of program

Research grants are awarded in this program to American universities to enable these universities to establish centers within both their own organizations, and in affiliate centers within foreign institutions to broaden collaborative research and research training in the biomedical fields.

2. Funds

In 1961, this program was administered by the National Institute of Allergy and Infectious Diseases and supported by six of the Institutes plus the Division of General Medical Sciences. This same situation existed in 1962 except for the absorption by Allergy of the support of Heart and Arthritis Institutes. In 1963, the program was administered by the Office of International Research, OIR, part of the Office of the Director, NIH. In 1964, OIR was incorporated into the GRS appropriation.

| | |
|---|---|
| 1962 obligations | $2,093,000 |
| 1963 obligations | 2,483,000 |
| 1964 obligations | 2,484,000 |
| 1965 obligations | 2,511,000 |
| 1966 obligations | 2,473,000 |
| 1967 obligations | 2,360,000 |
| 1968 estimates | 2,800,000 |
| 1969 estimates | 2,300,000 |

3. Present stage of development

The initial phase of the program devoted to the administratively complex task of developing foreign research resources in collaboration with selected foreign universities and research institutions has been completed in each of the centers. All centers are now actively engaged in specific research projects.

A substantial portion of current research is focused upon the demography, epidemiology, and ecology of disease states which are of concern to the United States and the host nation. A multidisciplinary approach is being developed within the several centers to study more effectively the complex biomedical problems which prevail at the foreign sites. As a consequence, professional staffs are being developed and trained to investigate, through a selective amalgamation of basic science, clinical and public health research methods, not only tropical diseases, but a wide variety of other disease states which exist in these countries. Accordingly, the scientific programs in each center will progressively encompass a wide spectrum of factors which directly or indirectly influence disease in the United States and abroad.

These programs include studies of environmental factors which may be related to the development and persistence of acute and chronic diseases. The presence of distinct ethnic and demographic groups in foreign areas permit studies in depth of physical and biomedical factors which may be involved in racial susceptibility to disease.

In addition to the research in progress and being planned, each university is creating an effective training program for U. S. citizens at both the domestic and overseas sites.

The cooperating institutions of the five International Centers now in operation are as follows:

| U. S. University | Foreign Cooperating Institutions |
|---|---|
| John Hopkins University---------- | All India Institute of Hygiene and Calcutta School of Tropical Medicine, Calcutta, India |
| University of California---------- | Institute of Medical Research, Kuala Lumpur, Federation of Malaysia |
| Tulane University---------- | Universidad del Valle, Cali, Colombia |
| Louisiana State University---------- | University of Costa Rica, San Jose |
| University of Maryland---------- | Institute of Hygiene and Lahore General Hospital, Lahore, West Pakistan |

4. Plans for the future

The 1969 President's budget will permit the continuation of the existing five centers.

## CLINICAL RESEARCH CENTERS

(Includes physical resources portions of program projects)

1. Purpose of program

To provide grants to non-Federal research institutions for the establishment and support of biomedical research resources centers. These centers make possible the performance of meritorious and complex clinical investigation in the preclinical, clinical, and health-related sciences. They provide the opportunity for precise observations and controls which are essential to studies with patients. These centers administrative may be viewed as (a) categorical and (b) general. The categorical centers are supported by the appropriate Institute and are concerned primarily with a specific category or type of disease, such as heart disease, toward which the work of the particular Institute is oriented. In the general clinical research centers program, which is supported by the Division of Research Facilities and Resources, the research activity is not focused primarily on a single Institute-related category of disease, but rather on categories of disease and on numerous areas of preclinical and clinical science. All centers consist of discrete facilities with specialized bed arrangements, core laboratories, and trained personnel. They use a multidisciplinary approach where investigators with varied interests and techniques share the center's facilities. The centers are highly conducive to the advancement of knowledge regarding human health and disease.

2. Funding of clinical research centers program (research center grants and physical resource component of program project grants)

(See the following table.)

3. Present stage of development

The Centers program had its inception in 1960 with an appropriation for general clinical centers. By the close of 1968 awards will have been made to approximately 91 general clinical research centers.

Seventy-eight categorical center grants had been awarded by the close of fiscal year 1967. As with the general clinical research centers program, the categorical programs have yielded important scientific accomplishments.

4. Plans for the future

The 1969 President's budget will be directed toward providing continuing and supplemental support to the centers receiving awards in 1968.

FUNDING OF CLINICAL RESEARCH CENTERS PROGRAM

Research center grants and physical resource component of program project grants

(In thousands)

| | Obligations, 1962 | Obligations, 1963 | Obligations, 1964 | Obligations, 1965 | Obligations, 1966 | Obligations, 1967 | Estimates, 1968 | Estimates, 1969 |
|---|---|---|---|---|---|---|---|---|
| Division of research facilities and resources | $22,123 | $17,374 | $27,057 | $26,906 | $28,500 | $28,463 | $30,443 | $35,677 |
| Child Health | ------- | ------- | ------- | 209 | 198 | 112 | 500 | 500 |
| Cancer | 805 | 4,437 | 4,849 | 4,898 | 7,283 | 1/ | 1/ | 1/ |
| Mental | 700 | 781 | 1,604 | 1,379 | 1,292 | ------- | ------- | ------- |
| Heart | 1,782 | 2,048 | 1,597 | 1,580 | 4,500 | 4,500 | 4,500 | 4,500 |
| Dental | ------- | ------- | ------- | 212 | 344 | 212 | 400 | 400 |
| Arthritis | 481 | 1,119 | 1,202 | 1,249 | 1,500 | 1,500 | 1,500 | 1,500 |
| Allergy | 500 | 237 | 852 | 949 | 881 | 1,099 | 1,100 | 1,100 |
| Neurology | 577 | 1,353 | 1,200 | 1,200 | 3,000 | 3,150 | 3,150 | 3,150 |
| Total | 26,968 | 27,349 | 38,361 | 38,582 | 47,498 | 39,036 | 41,593 | 46,827 |

1/ Beginning with 1967 the Cancer Institute funds are included in the table for specialized research centers.

## SPECIAL RESEARCH RESOURCES

1. Purpose of program

To provide grants to non-Federal research institutions for support of specialized facilities that provide the basic tools of research and specialized services necessary for the support of institutional research programs. Many areas of such research (such as determination of molecular structure or genetic codes) are enormously dependent upon computer resources, specialized instrumentation and/or commercially unobtainable biological materials. Since facilities to fulfill these needs are usually too costly or too extensive in capability to be assigned or managed by a single investigator, a Special Research Resource is established for use by a community of scientists; the basis for organization can be institutional, regional (city, state, section), or national. The needs of universities, hospitals, and other institutions for computer resources and centralized instrumentation facilities, for laboratories devoted to large-scale preparation of commercially unavailable biological materials, and other Special Research Resources is growing rapidly as the sophistication, capabilities, and costs of modern research increases. Such tools may consist of computers, highly trained technical staff, costly and complex instrumentation, or other aids to a large research operations.

2. Funds

| | |
|---|---|
| 1962 obligations | $4,329,000 |
| 1963 obligations | 6,117,000 |
| 1964 obligations | 5,077,000 |
| 1965 obligations | 8,169,000 |
| 1966 obligations | 10,618,000 |
| 1967 obligations | 10,850,000 |
| 1968 estimates | 10,850,000 |
| 1969 estimates | 10,850,000 |

3. Present stage of development

Program plans for 1968 call for the continuation of support for 51 established resources.

4. Plans for the future

The 1969 President's budget will provide for the continued funding of the existing specialized resources.

ANIMAL RESOURCES

1. Purpose of program

This program is designed to provide grants supportive of facilities which supply laboratory animals for institutional research and do research in laboratory animal medicine. Such grants support renovation and upgrading of animal facilities and research oriented toward improving the stock, health, and well-being of laboratory animals.

2. Funds

| | |
|---|---|
| 1965 obligations | $819,000 |
| 1966 obligations | 1,527,000 |
| 1967 obligations | 3,100,000 |
| 1968 estimates | 5,100,000 |
| 1969 estimates | 5,100,000 |

3. Present stage of development

Plans call for the continuation of support for 34 facilities and the funding of approximately 23 additional resources.

4. Plans for the future

The 1969 President's budget will provide for grants to approximately 20 new resources.

PRIMATE RESEARCH CENTERS PROGRAM

1. Purpose of program

To provide funds for the construction and basic operation of special research facilities or centers devoted to the advancement of all areas of knowledge on the biological characteristics of species structurally and physiologically similar to man throughout the entire lifespan of the subhuman primate. The objective is to acquire basic scientific information which will ultimately be useful in the prevention and treatment of human disease. Research facilities provided by this program are available to visiting scientists from all areas of this country and abroad.

2. Funds

| | |
|---|---|
| 1962 obligations | $9,495,000 |
| 1963 obligations | 4,444,000 |
| 1964 obligations | 6,194,000 |
| 1965 obligations | 7,000,000 |
| 1966 obligations | 7,000,000 |
| 1967 obligations | 9,000,000 |
| 1968 estimates | 10,500,000 |
| 1969 estimates | 10,500,000 |

3. Present stage of development

This program has six regional and one national center, the latter committed to research on the primate itself. The operating award is made each year after a detailed review of the proposed budget by the Division.

4. Plans for the future

The requested funds in the 1969 President's budget will provide for the support, maintenance and some supplementation of the existing seven centers.

PRIMATE RESEARCH CENTERS PROGRAM

1. Purpose of program

To provide funds for the construction and basic operation of special research facilities or centers devoted to the advancement of all areas of knowledge on the biological characteristics of species structurally and physiologically similar to man throughout the entire lifespan of the sub-human primate. The objective is to acquire basic scientific information which will ultimately be useful in the prevention and treatment of human disease. Research facilities provided by this program are available to visiting scientists from all areas of this country and abroad.

2. Funds

| | |
|---|---|
| 1962 obligations | $9,495,000 |
| 1963 obligations | 4,444,000 |
| 1964 obligations | 6,194,000 |
| 1965 obligations | 7,000,000 |
| 1966 obligations | 7,000,000 |
| 1967 obligations | 9,000,000 |
| 1968 estimates | 10,500,000 |
| 1969 estimates | 10,500,000 |

3. Present stage of development

This program has six regional and one national center, the latter committed to research on the primate itself. The operating award is made each year after a detailed review of the proposed budget by the Division.

4. Plans for the future

The requested funds in the 1969 President's budget will provide for the support, maintenance and some supplementation of the existing seven centers.

LEUKEMIA RESEARCH SUPPORT CENTERS

1. Funds for the program

The purpose of this program is to provide funds for rooms or nursing home type accommodations for leukemic patients being treated on a research basis in outpatient or special clinical units while the patients are ambulatory. These units ensure the more effective use of skills and release valuable research bed space, saving funds because the nursing home type accommodations cost less than regular research beds. The program supports the use of the plasmapheresis technique at additional institutions.

2. Funds

| | |
|---|---|
| 1966 obligations | $824,000 |
| 1967 obligations | 1,425,000 |
| 1968 estimates | 1,500,000 |
| 1969 estimates | 1,500,000 |

3. Present stage of development

In 1968 approximately 30 leukemia centers will be funded. Research on outpatient and inpatient basis, involving new drugs and blood platelet transfusions, will continue.

4. Plans for the future

The President's budget provides continuing support at the same level for 1969. Greater selectivity in funding is anticipated in 1969 with an expected increase in applications. Platelet replacement therapy in connection with the administration of control drugs will continue to be studied.

## HEART COOPERATIVE DRUG STUDY

1. Purpose of program

This program is designed and organized as a national cooperative study to determine whether several lipid-lowering drugs will, over prolonged periods of use, reduce the mortality or morbidity of coronary heart disease.

2. Funds

| | |
|---|---|
| 1965 obligations | $447,000 |
| 1966 obligations | 1,770,000 |
| 1967 obligations | 3,433,000 |
| 1968 estimates | 3,820,000 |
| 1969 estimates | 3,820,000 |

(Some additional funds for the study are included in direct operations amounts.)

3. Present stage of development

The feasibility of the study was affirmed over a two year period and the study proper initiated in 1965 with grants for the support of four participating clinics and coordinating center. During 1966 and 1967 the study was expanded to a full complement of 55 clinics.

4. Plans for the future

With the enrollment of clinics completed, the study is scheduled to complete a cohort of approximately 8,400 patients by June, 1969, and all patients will be followed for a period of 5 years. It is expected that the study will be completed in 1974 or 1975.

## PHARMACOLOGY-TOXICOLOGY RESEARCH

1. Purpose of program

The purpose of this program is to extend the program efforts of NIGMS in pharmacology and toxicology and to provide funds for the planning, initiation, and support of centers or large scale projects for research in areas of pharmacology and toxicology related to the use of drugs and chemical toxication. These programs are university based and located in appropriate academic and scientific environments.

2. Funds

| | |
|---|---|
| 1966 obligations | $1,000,000 |
| 1967 obligations | 3,358,617 |
| 1968 estimates | 3,500,000 |
| 1969 estimates | 3,500,000 |

3. Present stage of development

The program was initiated in 1966 and has grown during 1967 and 1968. Additional projects have been initiated at a modest level. Greater emphasis is being placed on clinical pharmacology and implications of new knowledge as it relates to man.

4. Plans for the future

The President's budget will provide continuing support for the program and other large scale projects currently being developed.

DENTAL RESEARCH INSTITUTES (CENTERS)

1. Purpose of program

The purpose of this program is to provide funds for the development and operation of dental research institutes as centers of excellence in the sciences related to oral health. Organized on an interdisciplinary basis, these institutes will support highly competent researchers as they deal with problems specifically related to oral health as well as perform research in the broader biological sciences and engineering and other physiochemical sciences. In addition, the institutes will offer a unique environment for the training of researchers and academicians.

2. Funds

| | |
|---|---|
| 1967 obligations | $2,996,000 |
| 1968 estimates | 3,000,000 |
| 1969 estimates | 3,000,000 |

3. Present stage of development

Currently, five dental research institutes are in various stages of development at the following universities: Alabama, Michigan, North Carolina, Pennsylvania, and Washington. It is expected that two or possibly three more centers will be initiated in 1968 and 1969.

4. Plans for the future

The President's budget provides continuing support for and expansion of this program in FY 1969.

## ANESTHESIOLOGY AND DIAGNOSTIC RADIOLOGY CENTERS

1. Purpose of program

The purpose of the anesthesiology and diagnostic radiology centers program is to provide research support for clinical and laboratory investigation related to teaching and patient care in these fields. One aspect of the program will be concerned with research leading to the development and evaluation of new techniques, bringing the fruits of biomedical engineering to the improvement of these specialties which are essential to all branches of health care.

2. Funds

| | |
|---|---|
| 1967 obligations | $500,000 |
| 1968 estimates | 1,000,000 |
| 1969 estimates | 1,000,000 |

3. Present stage of development

The initial year of the program provided for the development of one anesthesiology center, and one additional center has been established this year.

4. Plans for the future

The amounts in the President's budget provide for the continuing support of the two anesthesiology centers and the limited development of diagnostic radiology programs.

SPECIALIZED RESEARCH CENTERS

1. Purpose of program

The initial design of this program was to provide support for planning and operational grants for specialized centers in the Heart Disease, Cancer and Stroke areas. Each of the three Institutes involved makes awards in its own field for analyses of major problems and for the development of programs and resources, i.e., center establishments, to deal in depth with these disease areas.

2. Funds

See the table below.

3. Present stage of development

Since 1966 the Heart Institute has awarded or approved grants to 12 institutions for planning cardiovascular research and training centers. These awards are for programs of existing or potential excellence and are expected to compete for major operational center funds within the next several years. Cancer institute now supports 25 specialized research centers which are performing intensive, highly specialized clinical research or laboratory research relating to prevention, diagnosis, and treatment of cancer in man. In addition, the Cancer institute supports planning grants which are for costs incurred by institutions in the development of longterm plans for cancer research, training, and clinical services. Neurology had 11 centers in 1967; 15 will be in the planning stage for 1968.

4. Plans for the future

Funds in the President's budget will provide for continued planning support to the 1968 awardee institutions as well as a few new developmental awards. The long range plans of the Heart Institute provide for 12 specialized cardiovascular research and training centers during the next 5 years. Cancer plans to start one new center in 1969 in the radiation field, located in a geographical area not now serviced by any existing facility. Neurology plans an increase of six centers in 1969 making a total of 21.

| | Obligations | | |
|---|---|---|---|
| | Actual, 1967 | Estimate | |
| | | 1968 | 1969 |
| Heart | $658 | $800 | $1,050 |
| Cancer | 11,886 | 12,590 | 13,310 |
| Neurology | 1,450 | 800 | 900 |
| Total | 13,994 | 14,190 | 15,260 |

ENVIRONMENTAL HEALTH SCIENCE CENTERS

1. Purpose of program

The purpose of the environmental health sciences institutes is to establish university-based resources for both research and training which are embedded in the substance of graduate education. The programs embrace numerous facets of environmental health research--clinical and nonclinical activity, routine work and highly original studies, investigations by individuals and by teams, field studies, etc. They also permit advanced training in environmental health research in a depth that is relatively unavailable elsewhere. Institute grants may provide for common-use equipment, special laboratories, and salaries for a core group of scientists and administrative personnel. Individual studies are generally supported by funds from other sources.

2. Funds

| | |
|---|---|
| 1967 obligations | $2,529,000 |
| 1968 estimates | 3,000,000 |
| 1969 estimates | 3,000,000 |

3. Present stage of development

In 1968 the Division is supporting 5 Institutes that have operational status and 4 other institutions involved in pilot efforts.

4. Plans for the future

Funding at the same level in 1969 would permit continuation of the 5 ongoing Institutes and a transition to operational status for those currently active developmental programs that will require renewal support.

## REGULAR RESEARCH FELLOWSHIPS

NOTE: In this, and the following sections on Fellowships and Training grants, data through 1966 include amounts for the National Institute of Mental Health. Beginning with 1967, pursuant to the reorganization of the Public Health Service, the tables omit NIMH but include the Division of Environmental Health Sciences. The principal effects of this change are in Predoctoral Fellowships and in Training grants where there are reductions in 1967 over the amounts shown for 1966.

1. Purpose of program

The purpose of this program is to increase the supply of manpower available for research and teaching by providing qualified individuals with support for training in health related fields. There are three major categories or regular research fellowships; predoctoral, postdoctoral, and special.

Predoctoral fellowships provide assistance to individuals who have a bachelor's degree for further training leading to a doctoral degree. Postdoctoral fellowships support advanced training for an individual who has already earned a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. Special fellowships are designed to meet training needs not met by other fellowship programs, by supporting qualified investigators who require additional specialized training.

2. Funds

| | Predoctoral | Postdoctoral | Special | Total |
|---|---|---|---|---|
| 1959 obligations | $3,180,000 | $3,728,000 | $901,000 | $7,809,000 |
| 1960 obligations | 4,783,000 | 5,332,000 | 1,342,000 | 11,457,000 |
| 1961 obligations | 5,200,000 | 6,857,000 | 2,188,000 | 14,245,000 |
| 1962 obligations | 4,706,000 | 8,597,000 | 2,509,000 | 15,812,000 |
| 1963 obligations | 7,869,000 | 8,626,000 | 3,642,000 | 20,137,000 |
| 1964 obligations | 8,522,000 | 8,460,000 | 4,233,000 | 21,215,000 |
| 1965 obligations | 10,638,000 | 8,312,000 | 5,053,000 | 24,003,000 |
| 1966 obligations | 12,368,000 | 8,493,000 | 5,818,000 | 26,679,000 |
| 1967 obligations | 8,234,000 | 7,999,000 | 5,920,000 | 22,153,000 |
| 1968 estimate | 8,060,000 | 9,352,000 | 7,203,000 | 24,615,000 |
| 1969 estimate | 8,097,000 | 9,659,000 | 7,704,000 | 25,460,000 |

3. Number of awards

| | Predoctoral | Postdoctoral | Special | Total |
|---|---|---|---|---|
| 1962 actual | 1,469 | 1,229 | 273 | 2,971 |
| 1963 actual | 1,533 | 1,210 | 386 | 3,129 |
| 1964 actual | 1,665 | 1,181 | 422 | 3,268 |
| 1965 actual | 1,964 | 1,194 | 501 | 3,659 |
| 1966 actual | 2,323 | 1,287 | 582 | 4,192 |
| 1967 actual | 1,586 | 1,086 | 522 | 3,194 |
| 1968 estimate | 1,450 | 1,092 | 574 | 3,116 |
| 1969 estimate | 1,452 | 1,122 | 596 | 3,170 |

4. Present stage of development

The decrease in the total number of fellowships shown in this program in 1968 is due primarily to increases in the cost of stipends and an increase in the number of special fellowships which have a higher average cost than pre- and postdoctoral fellowships.

5. Plans for the future

The number of fellowships supported in 1969 will increase by 54 over the number supported in 1968.

## INTERNATIONAL POSTDOCTORAL FELLOWSHIPS

1. Purpose of program

This program provides awards to promising foreign scientists to support their training in the United States. While these awards contribute to the improvement of foreign research capabilities, the primary objectives of this program are domestic. These objectives are achieved by enabling foreign investigators to share their ideas and background with American colleagues, and by encouraging foreign scientists to participate in research bearing on American health problems. As this research is often continued and extended by the fellow upon return to his home, additional opportunities are created for future collaborative efforts in research endeavors of importance to the United States.

2. Funds and number of awards

| | Number | Amount |
|---|---|---|
| 1959 obligations | 45 | $345,000 |
| 1960 obligations | 52 | 400,000 |
| 1961 obligations | 92 | 700,000 |
| 1962 obligations | 91 | 700,000 |
| 1963 obligations | 172 | 1,198,000 |
| 1964 obligations | 177 | 1,199,000 |
| 1965 obligations | 184 | 1,177,000 |
| 1966 obligations | 166 | 1,199,000 |
| 1967 obligations | 155 | 1,200,000 |
| 1968 estimate | 154 | 1,380,000 |
| 1969 estimate | 176 | 1,411,000 |

3. Present stage of development

This program was established in Western Europe in Fiscal Year 1958 with 12 countries participating. Plans were made at that time for an orderly increase in the number of participating countries based on research potential and likelihood that returning fellows would use training in the United States. The increase in the number of countries participating has progressed according to schedule as follows: 1959, 30; 1960, 36; 1961, 40; 1962 and 1963, 41; 1964 and 1965, 42; 1966 through 1968, 43; 1969, 44.

4. Plans for the future

In 1969 approximately 176 fellows will be supported. This is an increase of 22 over the number supported in 1968.

## RESEARCH CAREER PROGRAM

1. Purpose of program

This program is designed to increase the number of stable full-time career opportunities for scientists of superior potential and capability in the sciences related to health. The program consists of two types of awards; career awards and career development awards. Career awards support established investigators of high competence for the duration of their careers. Career development awards support qualified scientists who have three years or more of relevant postdoctor research or professional experience and who require additional training in preparation for careers in independent research. Development awards are normally made for five years and may be extended for not more than a total of ten years.

2. Funds and number of awards

| | Number | Amount |
|---|---|---|
| 1962 obligations | 630 | $10,012,000 |
| 1963 obligations | 893 | 14,224,000 |
| 1964 obligations | 1,078 | 19,811,000 |
| 1965 obligations | 3,659 | 22,448,000 |
| 1966 obligations | 4,192 | 25,937,000 |
| 1967 obligations | 1,159 | 25,292,000 |
| 1968 estimate | 1,262 | 29,096,000 |
| 1969 estimate | 1,246 | 29,539,000 |

3. Present stage of development

Approximately 1,262 fellows will be supported in 1968. This is the sum of 168 Research Career Awards, a decrease of 8 from the 1967 level, and 1,094 Research Career Development Awards, an increase of 111 over 1967.

4. Plans for the future

During 1969, about 1,246 career fellowships will be supported. This represents a decrease of 13 Research Career Development Awards and a decrease of 3 Research Career Awards over the number supported in 1968.

TRAINING GRANTS

1. Purpose of program

These grants support training in specified aspects of health, medicine, and allied fields with the major objectives of (a) insuring an adequate supply of competent research and teaching manpower, and (b) facilitating within the student bodies of health-related professional schools the development of knowledge about special areas of disease that have particular significance. The training grant fulfills a dual function. Its funds underwrite certain expenses related to the specific training mission, including the provision of stipends to individuals selected for that training, except in (b) above. It also serves to create and maintain an atmosphere essential to the training by providing a focal point for the specific discipline or disease within the training institutions.

2. Funds

| | |
|---|---|
| 1959 obligations | $49,812,000 |
| 1960 obligations | 74,673,000 |
| 1961 obligations | 109,928,000 |
| 1962 obligations | 114,585,000 |
| 1963 obligations | 135,502,000 |
| 1964 obligations | 164,895,000 |
| 1965 obligations | 178,617,000 |
| 1966 obligations | 208,784,000 |
| 1967 obligations | 134,403,000 |
| 1968 estimate | 137,856,000 |
| 1969 estimate | 141,390,000 |

3. Present stage of development

The training programs of most of the NIH Institutes are directed toward the provision of adequate manpower for research in those disease areas for which they have assigned responsibilities. In contrast, the programs of the National Institute of General Medical Sciences are designed to support the fundamental sciences which undergird the disease-oriented interests of the categorical institutes. For this reason, their training programs cover the full range of the basic biomedical sciences.

In 1968 about 2,495 Training Grants will be supported.

4. Plans for the future

Emphasis will continue in areas where current and projected manpower shortages can be identified. Examples of such program areas to be supported by NIGMS include pharmacology and toxicology, the behavioral sciences, genetics, biophysics, biomedical engineering, and biostatistics. Areas of manpower shortages in programs supported by other Institutes include mental retardation, developmental and clinical pharmacology, aging, congenital malformations, virology, epidemiology, immunology and organ transplantation, artificial organs, orthopedics, urology and kidney disease, and neurology. Approximately 2,457 Training Grants will be supported in 1969, a decrease of 38 from the number supported in 1968.

## REGIONAL MEDICAL PROGRAMS

1. Purpose of program

These programs are designed to further research and treatment in heart disease, cancer and related diseases. Through grants, encouragement and assistance will be provided for the establishment of regional cooperative arrangements among medical schools, research institutions, and hospitals for research and training and for demonstrations of patient care.

The medical profession and medical institutions throughout the nation will be provided, thereby, a better opportunity to make available to their patients the latest advances in the diagnosis and treatment of these diseases without interference with the patterns of patient care or professional practice, with the methods of financing, or with the administration of hospitals.

2. Funds

| | |
|---|---|
| 1966 obligations | $2,657,076 |
| 1967 obligations | 29,256,000 |
| 1968 estimates | 53,786,000 |
| 1969 estimates | 68,922,000 |

3. Present stage of development

Current plans provide for planning grants and operational grants designed to link together the health resources of a region through cooperative arrangements intended to improve care within a region of all suffering from heart disease, cancer, stroke and related diseases. To date, this program has supported the establishment of 54 regionally-based programs devoted to planning activities.

4. Plans for the future

In 1969, in addition to planning activities in 54 regions and operational grants in 24 regions, it is expected that an additional 30 regions will have initiated or qualified for operational activities.

Highlights of Research Progress
during 1967

from

Division of Biologics Standards

Rubella Vaccine

Rubella, known to many as German measles, is one of the common contagious diseases. The virus responsible for the illness is worldwide in distribution. In the United States, major epidemics of rubella have occurred at 7-to-11-year intervals with lesser outbreaks during the intervening years. While the infection is most prevalent in school-age children, about 20 percent of all cases involve adults. Since the immunity conferred by rubella is probably lifelong, rubella in older individuals is thought to occur exclusively in those who escaped infection during childhood.

Rubella in children and adults is usually mild, resulting in an uncomplicated febrile illness characterized by rash and enlargement of the lymphatic glands. A significant number of persons have such slight symptoms that the infection is unrecognized. As a result, prior to 1941, many felt this virus to be inconsequential. However, in that year, the late Dr. Norman Gregg, an Australian ophthalmologist, revolutionized medical thought by observing that rubella infections in early pregnancy could cause grave defects in the unborn child. It is now well established that irrespective of the mildness of the mother's infection, the virus may cross the placenta to involve the fetus, causing serious damage manifested by: 1) spontaneous abortion, 2) stillbirth, or 3) live birth of children with blindness, deafness, heart disease, brain damage, and other major defects. It has been estimated that during the last epidemic in the United States (1963-65), rubella led to 30,000 fetal deaths and the birth of 20,000 deformed children.

In the past several years great strides have been made in rubella research. In 1966 two DBS scientists, Drs. Harry M. Meyer, Jr., and Paul D. Parkman, reported the attenuation or "taming" of the virus. They used their weakened virus (named HPV-77) to prepare the first effective experimental rubella vaccine. The HPV-77 virus was made freely available to investigators and pharmaceutical manufacturers here and abroad.

Vaccines prepared from this strain have now been administered to approximately 550 persons. No vaccinees have experienced adverse reactions from the vaccine, and more than 90 percent have developed antibodies indicative of

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Prepared January 1968 by the Division of Biologics Standards, Public Health Service, Department of Health, Education, and Welfare, in connection with fiscal year 1969 appropriation hearings.

immunity. Continued evaluation of the first children inoculated two years ago by the DBS team indicates that the level of vaccine-induced protective antibodies in their blood is unchanged. These observations encourage investigators to feel that the immunity conferred by the HPV-77 attenuated virus will be of long duration. Currently, trials with HPV-77 vaccines are under way or in advanced planning in the United States, Canada, England, France, Russia, Holland, Finland, Sweden, and Taiwan.

Studies have shown that the attenuated HPV-77 virus does not spread to contacts of vaccinees. This assurance of safety is being obtained under the various conditions of anticipated routine use: 1) in families; 2) in institutions housing infants, children, or young adults; and 3) in persons affected with major diseases such as tuberculosis. Irrespective of the circumstances, vaccinees experienced no fevers, rash, or other symptoms attributable to the attenuated virus, and their contacts remained uninfected.

The major research efforts of the DBS during the past year in this area have been directed toward: 1) determining the optimum degree of attenuation achievable with rubella viruses, 2) comparing the effectiveness of experimental vaccines produced in the several types of tissue cultures potentially useful for the preparation of rubella vaccines, and 3) bringing the new hemagglutination-inhibition (HI) test for rubella immunity into full practical use. In all of this work there has been extensive coordination and cooperation with similar efforts directed by the Vaccine Development Board of NIAID, several pharmaceutical manufacturers, and individual scientists.

Clinical and laboratory studies with rubella viruses representing different degrees of modification have established that higher tissue culture passage can result in an excessively weakened or overattenuated virus. Thus, candidate viruses for rubella vaccine production should represent an intermediate level of modification between unaltered virulent virus and overattenuated virus. Most investigators feel that the attenuated HPV-77 strain is the prime example of this ideal balance in modification.

Various groups have produced HPV-77-strain experimental vaccines in monkey kidney, dog kidney, and duck embryo tissue cultures. DBS investigators conducting clinical trials with these materials have found that the basic properties of the attenuated virus were unaltered by the type of tissue culture used. Thus, all of these tissue sources seem potentially useful for rubella vaccine production.

Because of the extensive clinical experience with other virus vaccines produced in chick embryo tissues, many workers have hoped to adapt rubella virus to growth in chick embryo tissue cultures. Recently, the DBS investigators succeeded in preparing several experimental vaccines in chick cell cultures. Clinical trials with these materials are in progress and will be compared with the results of studies with the experimental rubella vaccines produced in the other types of tissue cultures.

This past year, a simple blood test (HI test) to determine rubella immunity was perfected by Drs. Meyer, Parkman, and their colleagues in DBS.

This procedure has now moved from the DBS research laboratory to international application in vaccine development centers, hospitals, diagnostic laboratories, and doctors' offices.

In vaccine work, the HI test is used to identify appropriate candidates (persons susceptible to rubella) for vaccine studies and to determine the antibody (immunity) response induced by the vaccines. Because of its simplicity, precision, and speed, the HI test is expected to advance the target date of a final rubella vaccine by about one year, and to result in a saving of over a million dollars in government expenditures for rubella vaccine research.

In recognition of their contributions in developing the first safe and effective experimental rubella vaccine, and in discovering the rubella HI test, Drs. Meyer and Parkman jointly received the American Academy of Pediatrics 1967 E. Mead Johnson Award for pediatric research.

During the coming months it is anticipated that progressively larger rubella vaccine field trials involving thousands rather than hundreds of persons will be carried out. Also, many special studies with the HPV-77 vaccine will be continued, such as those dealing with high-risk groups. At present, there are no major obstacles visible, and capitalizing on the research achievements of the past year, the advanced stages in the development of the rubella vaccine are expected to proceed at a rapid rate.

Cholera

The progressive expansion of cholera-infected areas of the world in the past seven years, the recent occurrence of the disease in the Middle East, and its continued threat to Southeast Asian nations including Vietnam, have caused grave concern to national and international health authorities. In the opinion of many, the seventh pandemic of cholera may be in progress.

Although the threat of cholera can be minimized by improved sanitation, this approach to control of the disease is, for all practical purposes, unattainable in the foreseeable future in most of the countries at greatest risk. While modern treatment of cholera is highly effective, it cannot be readily provided in areas without adequate medical personnel and facilities for producing the large quantities of pyrogen-free intravenous solutions which are required for treatment. Accordingly, cholera vaccine continues to be the major weapon of public health for combating this disease.

Drs. John C. Feeley and Margaret Pittman, DBS, are collaborating with the Pakistan-SEATO Cholera Research Laboratory in Dacca to assess the efficacy of currently available vaccines and to determine the relationship between laboratory-assayed potency (e.g., mouse protection test) and serologic response and protection in man. This information, which is still being gathered, is essential for establishment of a meaningful standard of potency for cholera vaccine.

Results of field trials conducted to date show that while current

vaccines do give significant protection to the population as a whole, in the childhood population, which is at greatest risk, they are less effective and the duration of immunity is only a few months.

Improvement in the degree and duration of protection is imperative for effective use of the vaccine in children. The following DBS studies are currently directed to this problem. Since the cholera vibrio appears to produce the disease by means of a heat-labile antigenic toxin elaborated during growth in the intestinal tract, it may be possible to induce an "antitoxic" immunity to augment the "antibacterial" immunity provided by present vaccines. DBS efforts have resulted in methods for production of high yields of cholera toxin, and an experimental toxoid has been prepared which is 3 to 5 times more antigenic in animals than the toxin from which it was derived. In collaboration with scientists at Johns Hopkins University, this toxoid has been shown to offer significant protection in dogs against diarrhea caused by the choleragenic toxin. The protective effect of toxoid in dogs against Vibrio cholerae infection in currently under investigation.

In cooperation with the U.S.-Japan Cooperative Medical Science Program and the NIH Cholera Advisory Committee, research contracts have been initiated to enhance more rapid progress in purification of the toxin and, if animal studies continue to look favorable, the eventual development of a toxoid vaccine for human use.

DBS scientists are maintaining close contact and collaborating with workers in other research areas. For example, the testing of purified antigen and adjuvant-containing cholera vaccines offer considerable promise for improvement of the safety and efficacy of this product.

Oncogenicity in Relation to Vaccines

Studies of the relationship between certain viruses and the tumors they produce in experimental animals constitute a major portion of the DBS research program. Many mammalian and avian species harbor latent viruses, some of which have been found to have an oncogenic or tumor-producing potential. These findings are of particular consequence in biologics control since most virus vaccines are produced in mammalian or chick embryo tissue culture or in embryonated eggs.

When the oncogenic virus is a contaminant of the vaccine it can be eliminated by changing production techniques; however, if the vaccine virus itself has an oncogenic potential, the problem is infinitely more complex, requiring broad studies of long duration involving large numbers of animals to demonstrate the effects.

The first demonstration of the ability of simian virus 40 (SV40) to produce subcutaneous sarcomas in newborn hamsters was made by Dr. Bernice Eddy, DBS, in 1961. The capacity of SV40 and of certain adenoviruses to produce malignant tumors when injected into newborn hamsters has evoked wide interest in the scientific community and has stimulated a variety of investigations of the mode of action of these agents.

Although the relevance of tumors in newborn hamsters to the problems of human cancer has yet to be determined, the significance of the research under way in this area is unquestionably important. The newborn hamster is clearly the animal of choice for testing potentially oncogenic viruses of mammalian origin. The hamster test, in fact, has become the criterion in the appraisal of the safety of viral vaccines for human use.

All of the animal tumor viruses thus far encountered have the property of remaining in their hosts for long periods of time without causing any apparent disease. In this state they are latent (lying in wait) until induced to spring forth and manifest their malignant effects. SV40 and adenovirus 12 have been studied in detail by Dr. Eddy with respect to their propensity for remaining latent in human cell cultures, retaining throughout many passages the ability to produce fatal tumors when injected into newborn hamsters.

Immense progress has been made in the field of viral oncogenicity in the last several years. Adenovirus preparations, both oncogenic and non-oncogenic, have been found by electron microscopy to be contaminated by a small viral particle which is completely dependent on the adenovirus for its survival and reproduction. This virus, called adeno-associated virus (AAV) has been studied by several members of the DBS staff. Dr. Kendall Smith and his co-workers have studied its physio-chemical and biological properties. He has developed a fluorescing focus assay technique so that quantitative and qualitative studies of the virus can be performed without sole reliance on electron microscopic observations. This technique has proven to be 1,000 to 10,000 times more sensitive for the detection of AAV than electron microscopy or complement-fixation reaction.

It has been further shown that AAV has an inhibitory effect on the oncogenicity of the highly oncogenic adenovirus 12. Dr. Ruth L. Kirschstein and Dr. Smith showed that adenovirus 12 free of AAV caused tumors in 60 percent of inoculated newborn hamsters, whereas adenovirus 12 preparations containing AAV caused tumors in only 10 percent of such animals. In addition, the latent period for the appearance of tumors in animals receiving the adenovirus 12 preparation containing AAV was increased by 14 days over that in animals receiving the adenovirus 12 preparation free of AAV.

The possible relationship of a herpes-like virus to human leukemia and lymphoma is under study in many laboratories. Dr. Paul Gerber, DBS, has found that antibody is present in human and non-human primate species to an antigen prepared from African lymphoma cells containing the herpes-like viral particles. Dr. Gerber has succeeded in establishing continuous cultures of leuocytes from 6 normal human donors. The cultures grow as immature lymphoblastoid cells and four of the six contain the same herpes-like virus found in the Burkitt lymphoma in cell culture.

Through its research contract program, the DBS is investigating biological products, their ingredients, the cell substrates in which they are manufactured, and any additives which may be used, for freedom from oncogenicity in animal models. A wide variety of biological products are being tested for freedom from oncogenic properties in newborn hamsters. Involving many

hundreds of animals, each intensively observed for the duration of its lifetime, this study is believed to be essential to maintain confidence in the safety of the biological products licensed for human use.

In another project, also under the research contracts program, some of the chemically defined ingredients of biological products, such as preservatives, stabilizers, and other chemicals, will be investigated to verify their freedom from oncogenic effects. The tests will be conducted in several species of rodents and will include repeated injections of the substances at maximum tolerated dose.

A number of other projects are being organized to assess the carcinogenic or toxic effects of mineral oil emulsifier preparations on vaccines, to develop techniques for the detection of latent viruses in tissue cultures and other substrates for vaccine production, and to explore the usefulness of chromosomal analysis for discerning early changes in cells as indices of oncogenic effects.

Thus, the research contracts program, which permits the temporary expansion of facilities and personnel to attack problems of current importance, represents, insofar as possible, an extension of the interests and concern of DBS scientists for the safety of biological products.

In addition, the Division sponsored an international conference on "Cell Cultures for Virus Vaccine Production" in November 1967. Scientists from many countries presented information concerning the growth potential, oncogenic potential, and the safety and suitability for vaccine production of many types of primary animal cultures, human cell cultures, and continuous cell lines. This information will enable the Division to evaluate any potential viral vaccine produced in cell cultures not previously used for the production of viral vaccines.

Highlights of Research Progress
during 1967

from

National Cancer Institute

The National Cancer Institute was established 30 years ago to conduct and support research on causes, prevention, diagnosis and treatment of malignant diseases. Research is conducted at its Bethesda laboratories and in grant- and contract-supported institutions. Several broad areas for programmed research offering good possibilities of success have been defined--cancer cause and prevention, including the role of viruses, and treatment of cancer with special emphasis on a search for effective drugs. The NCI has organized Task Forces, composed of outstanding scientists from the Institute staff and institutions throughout the country, to identify new areas for programmed research on specific kinds of cancer. These include acute leukemia, the lymphomas and Hodgkin's disease, lung cancer, chronic leukemia and multiple myeloma, and breast cancer. In addition, other promising investigations deal with the immunological aspects of cancer and the basic changes that occur in the cancer cell. Highlights of research in these areas are summarized below.

Carcinogenesis

A major segment of cancer research is devoted to identifying the causes of cancer. Particular attention is given to possible cancer causing agents in the environment and the manner in which they act with the hope that control of exposure to these agents will prevent at least some forms of cancer.

Mycotoxins

Studies on mycotoxins (toxic products of fungi ) as possible sources of cancer causing agents, are being conducted by Dr. F. Blank and colleagues at Temple University, Philadelphia, and McGill University, Toronto, assisted by National Cancer Institute scientists. In a preliminary report they announced that a material causing cancer in mice has been found in Candida parapsilosis, a fungus known to cause skin disease in man. In the present study, 12 fungi known to infect skin were selected for testing, and extracts of each injected into mice. So far, only animals injected with extracts of Candida parapsilosis have developed subcutaneous tumors. Attempts are being made to repeat these observations and to carry out extraction and isolation procedures to identify the cancer-causing fraction.

Aflatoxins, products of the mold Aspergillus flavus, which grows on stored peanuts, cottonseed meal and other feedstuffs, are known to cause liver cancer or damage in several experimental animals. Various aspects

Prepared January 1968 by the National Cancer Institute, Public Health Service, U. S. Department of Health, Education, and Welfare in connection with 1969 appropriation hearings.

of aflatoxin activity were reported this year. For example, in an NCI study by Dr. J. Elis, injection with the most toxic component of aflatoxin, aflatoxin $B_1$, produced malformed embryos in hamsters, but the teratogenic influence was diminished by combining aflatoxin $B_1$ with DNA for 24 hours. Another study conducted under contract by Dr. Paul M. Newberne at the Massachusetts Institute of Technology was designed to determine effects of dietary supplements on the response of ducklings to aflatoxin-contaminated feeds. An increased sensitivity of ducklings to aflatoxin-contaminated peanut mold was observed when they were fed dietary supplements of amino acids arganine and lysine. Autoclaving the contaminated peanut meal destroyed or eliminated part of the aflatoxin activity.

A major achievement by contractors Drs. Gerald Wogan and George Buchi at MIT was the complete chemical synthesis of aflatoxin $B_1$. This should lead to the production of this compound in quantities sufficient for extensive research.

### Epidemiology

Other carcinogenesis studies have engaged the efforts of scientists working in the field of epidemiology. In the first of a series of statistical reports on patients treated at two large New York cancer centers, Dr. John W. Berg, NCI, found that with the exception of skin cancer, a second malignancy was not more likely to develop in patients with leukemia, lymphoma, or multiple myeloma (cancer of the bone marrow). Although the skin cancer rate for leukemia and lymphoma patients was seven times that of persons of the same sex and age distribution in the general population of New York, no single common cause of the increased risk of skin cancer could be identified.

Dr. Joseph F. Fraumeni and colleagues of NCI's Epidemiology Branch are among several groups of investigators who have reported that whatever the causes of human leukemia, the disease shows no evidence of being spread from person to person in the manner seen in the common infectious diseases. Last year they put in perspective a number of recent studies of the disease as it occurs in various populations, including "outbreaks" in specific localities. They found that, when considered from a statistical point of view, these clusters of leukemia cases were more likely rare events occurring by chance than interrelated cases of disease.

## Viruses and Cancer

### Special Virus Leukemia Program

NCI's Special Virus Leukemia Program in its 4th year, continues to coordinate an intensive research program aimed at the identification of a virus as a cause of leukemia or lymphoma in man, and the eventual control of this disease.

Virus-like particles of two different types can be seen with the electron microscope and in some cases isolated from patients with human leukemia and lymphoma. C-type particles are identical with those known to cause leukemia in laboratory animals, and are considered a prime candidate as a possible etiologic agent. During 1967, scientists continued to show that the plasma and some tissues of approximately 30 percent of human leukemia and lymphoma patients contain C-type particles. However, it has not yet been possible to induce these particles to persist or reproduce in an identifiable form in tissue culture, an important milestone needed for future work.

The second type of virus associated with leukemia and lymphoma is the herpes-type virus (HTV) similar in size and shape but not identical to those herpes viruses known to cause fever sores or shingles. Herpes-type viruses have been seen in at least 60 of the cultures of tumor cells that have been established from 105 leukemia and lymphoma patients. It is now possible to grow large quantities of these tumor cells and to recover large quantities of purified and concentrated HTV.

HTV has also been found in horses, frogs, toads, snakes, monkeys, and chimpanzees, and in people with noncancerous diseases as well as normal persons (at lower percentages than those associated with cancers). For example, Dr. Erling M. Jensen and colleagues at the John L. Smith Memorial for Cancer Research, Chas. Pfizer & Co., Inc. showed that HTV is distributed in patients with subacute leukemias as well as reticulum cell sarcomas, carcinomas of the esophagus and the lung and one non-cancerous growth. The wide distribution of HTV suggests the possibility that the particles may represent an unknown "passenger" agent.

Additional evidence for the presence (or former presence) of a virus in materials from leukemia and lymphoma patients comes from the detection of antigens associated with the virus. More extensive studies have confirmed earlier preliminary ones in which antisera prepared against pellets of human leukemia plasma known to contain C-type particles could detect the presence of immunofluorescent antigen in the white blood cells or bone marrow cells of about 60-70 percent of leukemia patients.

Antibodies found in the blood serum of normal as well as cancer patients are also being studied. These antibodies give clues to the prevalence of disease-associated antigens, possibly viruses. Dr. J. L. Ambrus, Roswell Park Memorial Institute, Buffalo, New York, reported that many normal persons appear to carry antibodies in their blood serum directed against acute myelocytic leukemia, Burkitt lymphoma and Hodgkin's disease, diseases considered likely to be caused by a virus.

Of particular interest in this study was the observation that almost no antibodies to these diseases were found in the population at ages when the risk of leukemia is highest.

Dr. George Klein and associates, Karolinska Institute, Stockholm, conducted a study of the antigens on the surface of Burkitt cells and found evidence that they are specific to the tumor. When biopsy specimens of Burkitt cells were tested against sera derived from Burkitt patients in regression after chemotherapy, positive immunofluorescent reactions occurred; no reactions occurred when normal bone marrow cells from donors of Burkitt cells were used. It is not yet known if the tumor-related antigen is virus-related or a virus.

Studies have shown that viruses, including the herpes simplex and certain oncogenic viruses can alter the chromosome pattern of cells and may affect specific chromosomes. In a study of five lines of virus-containing Burkitt cells, an identical marker chromosome was found in four of the cell lines and an extra C chromosome was found in four of the lines. It is not known if the C group chromosome abnormality indicates past or present virus infection, or if the marker chromosome is specific for Burkitt's lymphoma. Dr. Gertrude Kohn, and colleagues, Children's Hospital, Philadelphia, reported this study.

In another study at the same institution, Dr. Werner Henle and associates found chromosomal abnormalities characteristic of Burkitt cells in normal human leukocytes that were stimulated to grow in mixed culture with the Burkitt cells. They also found evidence for the transmission of the HTV antigen to the leukocytes. These results suggest the possible transmission of HTV from the Burkitt cells to normal cells, a significant step in establishing capability of transmission and replication of the virus in the human species.

The suspect HTV is being inoculated into many experimental animals or cultures of animal cells in an effort to demonstrate activity. In some cases infectivity or disease induction seems to have been produced. Recently, tissue cultures at Bionetics Research Laboratories, Kensington, Maryland were started from each of two chimpanzees following their inoculation with two human cell lines known to contain HTV. Both of the chimp lines were heavily infected with HTV, indicating, possibly, the transmission of human HTV for the first time to an animal recipient, an important step in producing larger amounts of virus required for studies underlying possible vaccine development.

Using extracts of human cells known to contain HTV, Dr. Sarah Stewart, NCI, confirmed her earlier observation that hamsters develop a progressive encephalitic syndrome leading to death following intracerebral inoculation with human cells or cell extracts known to contain herpes-virus. Investigators at Roswell Park Memorial Institute, Buffalo, New York have reported similar experience with newborn kittens.

Dr. Ben Burmester, USDA, East Lansing, Michigan, and Dr. Peter Biggs, London, reported evidence concurrently that Marek's disease, an acute form

of avian leukosis long suspected as being caused by a C-type virus is actually caused by a herpes-type virus. These findings provide another model system which may be expected to provide a guideline for the study of human HTV recovered from human neoplasms.

Dr. G. F. Rabotti, NCI, reported experimental conditions under which an oncogenic virus had crossed species lines and induced metastasizing tumors in primates. He first inoculated rhesus monkey cells in tissue culture with large doses of Rous Sarcoma Virus (RSV) which causes tumors in chickens. After two weeks, areas of fast-growing cells with altered structure were observed. When these transformed cells were injected under the skin or into the brains of newborn rhesus monkeys, the animals developed local sarcomas which eventually spread to other parts of the body. If similar optimal conditions can be developed for viruses suspected of causing human cancer, important evidence of their oncogenic potential in primates can be established.

Working along these same lines, Dr. Friedrich Deinhardt, Presbyterian-St. Luke's Hospital, Chicago reported that metastasizing tumors developed in marmosets (miniature monkeys) he had inoculated with RSV. Considerable effort on the part of many investigators continues in this field. A primate animal system is needed which, as in the polio story, can demonstrate association between human malignant disease and a virus isolated from human cancer tissue.

A new animal model system for leukemia studies is that developed recently in a strain of inbred guinea pigs. A virus associated with this leukemia has now been identified. This finding by Dr. S. R. Opler, Lenox Hill Hospital, and College of Physicians and Surgeons, Columbia University, is significant in view of the fact that the leukemia found in this animal species appears to be very similar to that seen in humans, including extensive involvement of nearly every organ system, with infiltration of leukemic cells.

## Solid Tumor Virus Program

NCI's Solid Tumor Virus Program coordinates an integrated study of the possibility that solid tumors in humans, like many in animals, are caused by viruses. Participating in much of this program's activities is the Laboratory of Infectious Diseases, NIAID.

Progress has been made under the Solid Tumor Virus Program in the isolation and purification of virus-related tumor antigens (T antigens) from cell cultures infected with human adenoviruses. First success has been with adenovirus type 12 T antigens. They will be used in attempts to detect specific adenovirus 12 antibody in sera of cancer patients.

A new approach to studies of viral-induced tumors involving the nucleic acids, DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) was provided by Dr. Maurice Green and colleagues, St. Louis University. This research is based on the knowledge that DNA controls the cell's biochemical processes and is passed on from generation to generation, and that information in DNA is transcribed to RNA which, in turn, translates it into the synthesis of proteins and enzymes.

Dr. Green reported that messenger RNA coded by DNA of an oncogenic human adenovirus is present in tumor cells of hamsters induced by this agent. The viral specific messenger RNA acts as a biological "footprint" and gives reliable information as to which of several adenoviruses was responsible for induction of the tumor.

Dr. Green and his associates are now working under contract with the Solid Tumor Virus program to extend their findings to studies of human tumors. Using techniques developed primarily in their laboratory, they are examining large numbers of representative types of human tumors for the tell-tale presence of nucleic acid materials specific for certain viruses, particularly the human adenoviruses. They are labeling RNAs in surgically removed human tumors with radioactive RNA precursors, extracting the labeled RNA, and incubating it with a purified adenovirus DNA. A positive reaction--the formation of a DNA-RNA complex--will indicate the presence of viral-specific RNA and will provide evidence that the test adenovirus had been involved in the tumor.

## Nucleic Acid Studies

Much other research is being conducted on the nucleic acids. Changes occurring in these chemical components of cells or in their expression are important in the events leading to malignant transformation.

The nucleic acids of viruses that cause cancer in laboratory animals are being studied to determine their properties and their mode of action. In one study, Dr. Samuel W. Luborsky, NCI, and contractors at Melpar, Inc., developed a method of producing radioactively labeled polyoma virus DNA. Labeled DNA is needed to provide a rapid and sensitive assay for the presence of the virus, especially for studies regarding the fate of the viral DNA in the cell it infects.

Dr. Andrew C. Peacock, Chemistry Branch, NCI, and his associates are among the many investigators engaged in developing methods for the separation and characterization of RNA. Using a technique in which particles migrate in an electric field, the NCI scientists have separated at least 30 different kinds of RNA from rat liver, kidney, and brain tissue. The use and further development of this method will significantly increase the ability of scientists to characterize and elucidate the molecular basis of a variety of biological phenomena, including carcinogenesis.

Treating Leukemia

Drug Studies

At the National Cancer Institute, current plans for treating human leukemia are being shaped by concepts derived from observations of leukemic cells in animals. One of these concepts is that "100 percent kill" of leukemic cells is necessary to achieve cure. This concept was developed by Dr. Howard Skipper, an Acute Leukemia Task Force member from the Southern Research Institute, Birmingham, Alabama, and by former NCI staff members, Drs. Emil Frei III and Emil J. Freireich, both now at the M.D. Anderson Hospital and Tumor Institute, Houston.

A second concept is based on the observation by Dr. Skipper and his associates that a given dose of a drug kills the same percentage of cells no matter how many cells are present. This means, as has been shown in animal experiments, that the most effective drug treatment is one given early in the course of the disease when leukemic cells are comparatively few. Animal experiments have also shown that drugs should be administered in short, intensive courses.

Applying these concepts to human leukemia, scientists have estimated that it takes human leukemic cells about 4 days to double in number and that the lethal number of leukemic cells is $10^{12}$ or 1,000,000,000,000 cells. Further calculations indicate that it would require about 160 to 170 days for one cell, doubling every four days, to develop to this number.

Efforts are being made to achieve "100 percent kill" using large intermittent doses of combinations of drugs. The four drugs used in one study at the National Cancer Institute to treat childhood acute leukemia are vincristine, prednisone, 6-mercaptopurine, and methotrexate, given on an intermittent schedule for up to 14 months along with supportive therapy as needed.

Recent results of this continuing study, reported by Dr. Edward S. Henderson, NCI, estimate the median survival of 35 patients at three years from the start of a 4-drug treatment. Sixteen of 35 previously untreated children with acute lymphocytic leukemia are surviving for periods up to 3 years and 2 months following the start of intensive drug therapy. The investigators estimate about a 3-year median survival time for the group, a year longer than achieved in previous combination chemotherapy studies by the Institute. It is 12 times the life expectancy of children with leukemia 20 years ago.

Large doses of methotrexate given intermittently, and supplemented as needed with other agents were used to maintain remissions in 15 children with acute lymphocytic leukemia by I. Djerassi and colleagues, Children's Hospital of Philadelphia, Philadelphia, Pa. Drug doses were based on

biochemical models of the mechanism of action and resistance to this agent and were given with safety. Five of 7 patients are alive with an average of 37 months and 7 of a second group are alive at present for an average of 26 months.

## Supportive Therapy

The leading causes of death in acute leukemia patients are infection and hemorrhage, brought about because the leukemic process and the drugs used to fight the disease lower the patient's number of important blood elements--granulocytes, infection-fighting white cells, and platelets necessary for clotting. Methods which help prevent infection and hemorrhage are applied as supportive therapy.

As part of the effort to obtain large numbers of blood cells for transfusion into leukemia patients, NCI, in collaboration with International Business Machines, has been developing a blood-cell separator, a machine capable of separating granulocytes and platelets from a donor's blood on a continuous flow basis, in vivo. The donor's blood flows through the machine where it is centrifuged to separate out the various blood fractions, and then the red blood cells are returned to the donor, enabling him to give blood often without ill effects.

Preliminary results are now promising on the separation of granulocytes and platelets. Over 135 trial runs have been made on dogs. More recently, the separator has been used on humans.

A continuing study of the "Life Island," a plastic enclosure that isolates the patient in a relatively germ-free environment, has shown that the incidence of infection of patients within the isolator is reduced. It has been possible to maintain a patient for long periods (at least 3 months) in the isolator. Whether drug toxicity is reduced remains to be seen but thus far the impression is that toxicity is somewhat less even when large doses of drugs are used.

To enlarge on the idea of the Life Island, plans are being formulated for "laminar flow rooms," rooms with relatively germ-free circulations of air, where leukemia patients can be confined with lessened chance of infection.

## Radiation Treatment

In a few studies, radiation is being used to treat some leukemia and lymphoma patients. Dr. Ralph Johnson, Radiation Branch, NCI, and his colleagues have observed objective responses and complete clinical remissions in patients with lymphosarcoma. Excellent improvements have also occurred in the blood of patients with chronic lymphocytic leukemia (CLL).

Dr. Robert A. Kagan, NCI, reported a way to evaluate treatment by whole-body irradiation given to patients with CLL, using an in vitro test. Known as the lymphocyte transformation test, it distinguishes malignant lymphocytes from normal ones in patients with CLL. Using this test Dr. Kagan found that the tumor cell population is markedly reduced in patients undergoing fractionated total-body irradiation, coincident with regression of the disease.

Treating Hodgkin's Disease

Radiation

Hodgkin's disease, cancer of the lymph system, now appears curable in more than 50 percent of cases that are treated aggressively in early stages with intensive doses of radiation.

Dr. Johnson, NCI, reported that Hodgkin's disease is not only curable in patients with "early" disease but also that the potential exists for achieving cures in patients with more advanced disease. He bases his belief on evidence that: local manifestations of Hodgkin's disease can be eliminated for long periods by irradiation; the pattern of spread of Hodgkin's disease can be predicted, permitting "prophylactic" irradiation of lymph node areas known to be at "high risk"; and tumoricidal doses of radiation can be administered with relative safety to multiple areas of the body.

During the past several years, this type of extended intensive irradiation has been given to 40 patients at NIH with a minimum of serious side effects. Thirteen of 14 patients with advanced Hodgkin's disease went into complete remission after high dose extended irradiation. Median duration of remission is approximately one year.

Drugs

Like acute leukemia, Hodgkin's disease responds very effectively to combination chemotherapy. Preliminary findings from studies at NCI indicate that a higher percentage of complete remissions and longer durations of unmaintained remissions can be achieved with drug combinations than with single compounds used one after the other.

Four-drug treatment produced encouraging results against advanced Hodgkin's disease in 25 of 30 patients studied by Dr. Vincent T. DeVita, NCI, and Dr. Arthur A. Serpick, U. S. Public Health Service Hospital, Baltimore. The rate of complete remission, or temporary disappearance of all evidence of cancer, was more than twice as high, and the length of remission 3 to 4 times as long as is ordinarily achieved with single drug therapy. The regimen consisted of six 28-day courses of treatment using nitrogen mustard, vincristine, methyl hydrazine derivative (MIH) and prednisone.

The sequential use of cyclophosphamide and the vinca alkaloids produced partial or complete remission in 75 percent of a group of patients with advanced Hodgkin's disease, according to a large cooperative study conducted under NCI sponsorship. The study indicated that the drugs are much the same in effectiveness and that one does not interfere with another's activity. The study also indicated that remission duration was significantly longer if remissions were maintained with an alkylating agent given orally.

Since drugs used to treat Hodgkin's disease appear to decrease the patient's symptoms and the size of his tumor, they may be helpful in combination with x-irradiation, usually the treatment of choice for early disease. It is hoped that a combination of radiotherapy and chemotherapy may offer better results than either method alone and that chemotherapy may make patients more susceptible to curative treatment with X-ray.

New Drugs

A major goal of NCI's Chemotherapy Program is the search for new agents. Several relatively new drugs have shown, during the past year, further clinical activity against leukemia and other forms of cancer.

For example, the usefulness of dibromomannitol, a drug developed in Europe for the treatment of adults with chronic myelogenous leukemia, has been confirmed in studies by Dr. Edward L. Cahn and colleagues at NCI. Of 26 patients receiving dibromomannitol for longer than 3 weeks, all showed some degree of benefit from the drug by the end of 6 weeks. At 12 weeks, 6 had achieved complete and 17 partial remission of the disease. Toxic side effects were strikingly few and the percentage of patients responding to treatment compared favorably with the response expected following treatment with Busulfan (Myleran), the drug most frequently prescribed for CML patients.

Members of the Acute Leukemia Group B of the Cancer Chemotherapy Program reported results of a study using the drug melphalan to treat patients with multiple myeloma, cancer of the plasma cells found in the bone marrow. Melphalan produced significant subjective and objective response and was effective in prolonging survival in a high percentage of patients studied. More than half of 53 patients responded to the drug, the most striking effect being a rapid decrease in bone pain. The 50 percent survival time of patients was 23 months, as compared to 8 months without melphalan treatment. Until this study, no drug had been established as producing good responses in a high percentage of patients or prolonging survival time.

One study highlighted the potential risk of drug therapy in certain patients. Dr. John Bailar, NCI, reported the results of a prospective study by members of the Veterans Administration Cooperative Urological

Research Group. In treating 2500 patients with cancer of the prostate these physicians found that estrogen therapy and/or orchiectomy (surgical removal of the testes) results in a slight reduction in deaths from prostate cancer but substantially increases the risk of death from cardiovascular diseases.

Animal studies have provided hope that the usual toxic effects of a potential anticancer agent, the antibiotic streptozotocin, can be prevented. Dr. Philip Schein, NCI, and colleagues at the Hazleton Laboratories of Falls Church, Va. report that injection of nicotinamide into mice and rats ten minutes prior to administration of streptozotocin, apparently protects the insulin-producing cells of the pancreas, thereby preventing diabetes in the animals. Leukemic mice receiving the vitamin-drug sequence had a 20-30 percent longer life span than leukemic animals treated with effective doses of the drug alone. Similar results were subsequently demonstrated in dogs and monkeys by NCI supported collaborative research. Investigators hope now to try a combination of nicotinamide and BCNU, another drug that has appeared very promising in tests against animal cancer but whose use in human cancer has been curtailed because of its toxicity.

Immunological Studies

Because of evidence that host defenses may play a significant role in response to therapy, immunological aspects of cancer are being investigated. Dr. Harley A. Haynes and colleagues, NCI, reported results of a study to clarify the relationship among various immunologic functions in 50 patients with newly diagnosed, untreated Hodgkin's disease.

The results so far challenge long-held beliefs that in these cancer patients there is a significant impairment of cellular immunity called delayed hypersensitivity. The NCI scientists found that patients with localized disease had nearly normal sensitivity as demonstrated by the incidence of positive skin reactions following injections with small amounts of foreign substances. Patients with more advanced stages of the disease demonstrated progressively impaired reactivity, but not so profound as had been observed in treated patients. The investigators believe that the depression of delayed hypersensitivity is probably a consequence of the disease process and not a causative factor in the development of Hodgkin's disease.

Along this same line, investigators in NCI's Dermatology Branch found that in patients with mycosis fungoides, a kind of lymphoma that originates in the skin, immunologic reactivity remains normal throughout its course.

The immune response of experimental animals is also under study. Dr. A. Fefer and colleagues at NCI and Microbiological Associates, Inc., reported that a strong immune response may be responsible for the

regression or disappearance of tumors induced in mice by the Moloney sarcoma virus, although it may not prevent the tumors from being induced in the first place.

One of the goals of research on immunological aspects of cancer is the prevention of the disease using vaccines or other methods of stimulating the production of antibodies, disease-fighting substances produced by the body in response to invasion by antigens.

At NCI, investigators are studying the in vitro synthesis of immunoglobulins (antibody-containing proteins) by human cell lines. Dr. Ira Finegold and colleagues, reported the synthesis of a wide range of normal-type immunoglobulins in 19 of 30 cell lines grown in continuous culture. There was evidence that one cell population may produce several immunoglobulins. These studies may lead to large-scale synthesis of specific antibodies for use in protection against disease in man, and should contribute to a better understanding of normal and abnormal immune processes.

Breast Cancer Studies

Breast cancer is the most common single type of cancer in women. In 1966, the National Cancer Institute established the Breast Cancer Task Force to coordinate an intensive research attack on this disease. During the past year, the Task Force has been planning, organizing and initiating research projects, most of them to be carried out under contract. In the meantime, results have been reported on two long-term studies of the value of mammography (X-ray examination of the breast) to detect breast cancer.

In a contracted study by the Health Insurance Plan of New York periodical screening of women for breast cancer, using mammography and clinical examination, has been found useful in detecting the disease in its earliest stages. In the screened group of more than 20,000 women, 64 percent of the cancers detected were in the earliest stage, while in an unscreened control group 41 percent were in this stage. It is estimated that breast cancer was detected 21 months earlier by screening. Mammography was found most useful in women over 50, in large breasts of the fatty type, and when the tumor was in the lower half of the breast. Clinical examination was particularly effective in women under 50 and in small breasts of the glandular type. In addition, it was found that a long menstrual history associated with years of continuing high estrogen levels appears to play a role in a high incidence of breast cancer. The study is a long-term one to establish whether earlier detection will, in fact, improve the mortality picture in breast cancer. Several more years of following the patients participating in the study will be required before a definitive answer will be in hand. William Haenszel, Biometry Branch, NCI, and project officer on this contract is providing expert guidance.

Dr. J. Gershon-Cohen and colleagues at Albert Einstein Medical Center, Philadelphia, reported results of mammographic screening of 1120 women over 10 years. Cancer was found in 33 women and bilaterally in 3 of the women during subsequent examinations. The cancer was in its early stage in 70 percent of the women. Eighty percent of these women survived five years, compared with the usual 45 percent of women who discover their own lesions without benefit of screening.

Dr. Marvin Zelen, NCI, developed a statistical method for studying the natural history of chronic disease and reported its application to breast cancer. Four important disease-related variables were studied in a series of 467 breast cancer patients and statistics on the diagnosis, survival and death from breast cancer in these patients were analyzed. The study highlighted factors of importance in prognosis and evaluation, and recommended a modified form of auxiliary therapy in surgically treated breast cancer patients.

Highlights of Research Progress
during 1967
from the
National Heart Institute

## Atherosclerosis and Coronary Heart Disease

Elevated blood cholesterol levels have been the factor most consistently associated with increased susceptibility to coronary heart disease (CHD). However, two other blood lipid fractions also appear to be important determinants of heart disease risk, NHI grantees report. Elevated blood levels of triglycerides (neutral fat) or a high ratio of low-density lipoproteins appear to increase heart-disease risk in subjects with normal cholesterol levels. If two or three blood-lipid fractions are elevated, the risk is correspondingly higher.

These preliminary findings are drawn from a study of 3,182 men aged 39-59 at entry and found free of coronary heart disease at that time. The study, begun in 1960, is attempting to determine differences between those who subsequently develop CHD and those remaining free of it in order to define those factors that affect susceptibility.

The salient findings, expressed in terms of the annual rate of CHD per 1000 subjects at risk, were these:

.Among men with cholesterol levels exceeding 259 mg. per 100 ml. the CHD rate was approximately 4 times that of men with levels below 220 (17.5 vs. 4.4).

.Among men with triglyceride levels exceeding 176, the CHD rate was nearly 3 times that of men with levels below 100 (14.9 vs. 5.2).

.Among men with low-density to high-density lipoprotein ratios exceeding 2.35, the CHD rate was more than double that of men with ratios below 2.01 (14.5 vs. 6.3). A preponderance of low-density lipoproteins is thought to be atherogenic because this lipoprotein class provides the transport vehicles for most of the cholesterol and triglycerides of the blood.

The CHD rate of 14.5 per 1000 for men with elevated cholesterol rose to 20.8 if triglycerides were also elevated and to 24.6 if all three fractions were elevated.

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The grantees noted, however, that a large proportion of men developing CHD failed to exhibit elevated blood-lipids. Another risk factor appeared to be operating in this population group to increase risk whether or not blood lipids were elevated and to escalate risk in those also having blood-lipid abnormalities. This risk factor is a personality pattern, called type A, characterized by inordinate ambition, aggressiveness, and a strong sense of time urgency.

Men with this hard-driving behavioral pattern have developed CHD with about 3 times the frequency of their more placid counterparts (classified as personality type B). Moreover, of the 28 study subjects who died of CHD over a 5-year period, 25 were type A and only 3 type B. Autopsy studies performed on 51 of 82 subjects dying of all causes during the study indicated that coronary atherosclerosis in the type A subjects averaged nearly twice as severe as that in type B subjects. The disease process in the two groups appeared to differ in degree rather than in kind.

These findings were reported by Drs. R. H. Rosenman, M. Friedman, R. Straus, M. Wurm, and R. Kositchek of Burbank, California, Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco, California.

Most therapeutic diets and drugs for the management of elevated blood lipid levels have been aimed at the reduction of blood cholesterol. However, elevated blood cholesterol is only one facet of the larger clinical problem of hyperlipidemia. In turn, NHI studies have shown, hyperlipidemia is not a single entity, but at least 5, several of which include elevated cholesterol as one of their manifestations.

The NHI studies have resulted in a rational system for identifying and classifying hyperlipidemias on the basis of serum lipoprotein patterns, easily obtained by low-cost electrophoretic techniques. Under this system, most patients with elevated blood lipids fall conveniently into one of the categories of hyperlipoproteinemia designated as types I-V. This is an important step toward a more systematic approach to clinical management, for standard "cholesterol lowering" regimens are not uniformly effective against all types of hyperlipoproteinemia. In fact, lumping patients with different types of hyperlipoproteinemia under the general heading of "hypercholesterolemia" may be responsible in large measure for the wide individual variability in response to diet or drug regimens frequently observed in clinical trials.

Currently Dr. R. I. Levy and co-workers in the NHI Laboratory of Molecular Diseases are determining which mode of therapy is best suited to each of the five types of hyperlipoproteinemia. The two most common are type II and type III.

Type II is characterized by a relative excess of low-density lipoproteins. It may be an inherited condition, of dietary origin, or it may be a secondary manifestation of certain other metabolic disorders, especially hypothyroidism. It is probably responsible for most cases of "hypercholesterolemia" that the physician is called upon to treat. Type III, though less common than type II, is by no means rare. It, too, is characterized by an excess of low-density lipoproteins, especially the very-low-density ones that transport chiefly cholesterol and triglycerides in the blood. Both of these blood lipids are commonly elevated in type III patients. Both types of hyperlipoproteinemia are associated with accelerated development of atherosclerosis. In addition, a common characteristic of both types, if severe, is the appearance of fatty deposits called xanthomas in various soft tissues of the body, particularly around tendons of the hands and feet.

Nineteen patients with each type have been treated with a therapeutic diet containing 40 percent of total calories as fat, chiefly polyunsaturated; 40 percent carbohydrate; and 20 percent protein. Cholesterol intake was limited to 300 mg. per day.

In type II patients, average blood cholesterol levels fell from 438 to 330 and blood triglycerides decreased slightly. In type III patients, cholesterol fell from 486 to 228 and triglycerides from 650 to 194. Thus, the therapeutic diet substantially improved the blood-lipid pattern in type II and nearly normalized it in type III.

Further blood-lipid reductions were achieved when the therapeutic diet was supplemented with the lipid-lowering drug clofibrate. In type III patients, the drug reduced cholesterol by an additional 14 percent and triglycerides by 22 percent. The response was still more dramatic in type III patients: cholesterol fell by an additional 29 percent and triglycerides by 44 percent. Therapy resulted in rapid regression of xanthomas in type III patients.

These findings were reported by Dr~. R. I. Levy, S. H. Quarfordt, H. R. Sloan, W. V. Brown, and D. S. Fredrickson of the Laboratory of Molecular Diseases, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

Some scientists have maintained that attempts to prevent atherosclerosis are most likely to succeed if initiated by pediatricians. Some support for this contention in the case of infants born of mothers with hereditary hypercholesterolemia is provided by findings reported by Drs. L. A. Lewis and H. B. Brown, of the Cleveland Clinic, and by Dr. J. G. Green, of NHI.

Three of the six infants exhibited abnormally high blood cholesterol levels within a week of birth and the other 3 were hypercholesterolemic when first examined at 3, 13, and 28 months of age, respectively. When maintained on the usual diet for 8-36 months, all children exhibited increasing blood cholesterol levels. In 2 children the levels rose above 250 mg. per 100 ml. and in the other 4 above 300 (the normal level for children under ten is 165).

When the children were placed on diets low in saturated fat and cholesterol and high in unsaturated fat, their blood cholesterol levels fell by an average of 21 percent and have been maintained at these lower levels. The dietary modifications have not interfered with normal weight gain and growth.

Polyunsaturated fats (liquid fats derived chiefly from vegetable or marine oils) tend to reduce blood cholesterol levels, but the mechanism by which they do so has not been adequately defined. Studies by Dr. W. E. Connor and co-workers, of the University of Iowa, indicate that polyunsaturated fats substantially increase the excretion of cholesterol derivatives (neutral sterols and bile acids) in the feces. These losses may be made good, in part, at the expense of blood cholesterol.

In these studies healthy subjects were fed cholesterol-free formula diets rich in saturated fat (cocoa butter) or polyunsaturated fats (corn oil) over 3 dietary periods of 3 weeks each. The subjects started on cocoa butter, were switched to corn oil, then back to cocoa butter.

During the first dietary period, blood cholesterol averaged 222 mg. per 100 ml., fell to 177 on the corn oil diet, then climbed to 225 when the cocoa butter diet was resumed. During the first dietary period, daily fecal sterol excretion averaged 744 mg. per day, climbed to 953 with corn oil, then fell to 672. Corn oil also increased the excretion of bile acids.

The total sterol excretion during the corn oil diet was approximately twice as high as the amount of cholesterol calculated to have left the blood. This suggests that polyunsaturated fats reduced tissue cholesterol levels as well as blood cholesterol.

Other NHI grantees studied the distribution of cholesterol in various tissues of 4 animal species--two (rats and dogs) known to be resistant to diet-induced hypercholesterolemia and atherosclerosis, the other two (prairie dogs and rabbits) known to be highly susceptible.

In these studies, conducted by Dr. W. Hollander and co-workers, of the Boston University Medical Center, half of the animals of each species

received a low cholesterol diet for 3-12 months, the other half received a diet high in cholesterol derived from egg yolk.

When animals on the low-cholesterol diet were sacrificed, the scientists found no significant species differences in the cholesterol content of various organs and tissues.

Among the animals fed high-cholesterol diets, the two species resistant to atherosclerosis (rats and dogs) showed a moderate increase in the cholesterol content of the liver. But in all other organs and tissues studied, the cholesterol content did not differ significantly from that observed in the animals on the low-cholesterol diet.

However, in the susceptible species (prairie dog and rabbit), the high-cholesterol diet substantially increased the cholesterol content of all tissues and organs except the brain. When some of these rabbits were switched from high-cholesterol diets, the excessive tissue cholesterol levels reverted to normal in all tissues except two: the cholesterol content of skin and of blood-vessel tissues remained elevated.

Apparently, resistance or susceptibility to hypercholesterolemia and atherosclerosis is determined in part by capability of the tissues of the body to handle cholesterol presented to them by the blood. Not only are there species differences in this capability, but within a given species some tissues and organs can cope with excessive cholesterol better than others. In susceptible species, the blood-vessel wall appears especially vulnerable to a cholesterol glut; and the cholesterol, once gaining entry, tends to stay.

A high proportion of patients with atherosclerosis exhibit a latent abnormality of carbohydrate metabolism that may accelerate the development of their blood-vessel diseases, according to Drs. P. T. Kuo and L. Y. Feng, of the University of Pennsylvania.

After consuming a meal high in carbohydrate, especially refined sugars, such patients show moderate to marked increases in plasma insulin activity, followed by increased production of very low density lipoproteins (VLDL) by the liver. Since this lipoprotein class provides the carrier vehicles for most of the cholesterol and triglycerides (neutral fat) of plasma, both of these blood lipid fractions are elevated and the elevations sustained by high-carbohydrate diets.

Of 286 randomly selected patients with atherosclerosis, 234 (91.6%) exhibited abnormally high VLDL synthesis and elevated blood lipid levels while subsisting on a diet containing 35-40 percent of its calories as carbohydrate. Subsequent studies in 20 of these indicated that sucrose, a simple sugar, provoked greater increases in plasma insulin activity and VLDL synthesis than did starch, a more complex carbohydrate.

The scientists found that the abnormality in carbohydrate metabolism and the patients' blood lipid levels could be kept under control by diets limiting daily carbohydrate intake to 125-150 gm., very low in sugar and alcohol, and low in short-chain triglycerides.

Autopsy studies of the development of atherosclerosis in the coronary arteries of individuals of widely different geographic and ethnic groups indicate that the distribution pattern of atherosclerotic deposits is distinct for each of the 3 coronary arteries. These three patterns held whether the subject was male or female, young or old, or from high-risk or low-risk populations.

In the circumflex branch of the left coronary, for example, lesions occurred with greatest frequency in the first 2 cm. of the artery, then declined sharply and progressively in frequency over the next 4 to 5 cm. Distinct distribution patterns were also observed in the left anterior descending branch and in the right coronary artery. In general, atherosclerosis usually attacked segments very close to the origin of the artery, leaving the "downstream" portion of the artery and it's branches relatively unscathed.

The distribution of lesions was the same whether observed early in the course of the disease, when they were usually fatty streaks, or in its advanced stages (fibrous, calcified plaques).

The results were obtained in autopsy studies of nearly 3,000 persons, aged 10-69 years, that included New Orleans whites and Negroes, Chilean whites, Guatemalan Indians, Brazilian whites and Negroes, and South African Bantu. They were reported by Dr. M. R. Montenegro, of Faculdade de Ciencias Medicas E. Biologicas de Botucatu, Sao Paulo, Brazil, and Dr. D. A. Eggen of Louisiana State University.

The results suggest that while ethnic factors and mode of life may affect the rate of development of coronary heart disease and its ultimate severity, its pattern of development is probably strikingly similar all over the globe.

Atherosclerotic deposits obstructing the coronary arteries and thus impeding bloodflow to the heart muscle itself are usually confined to the first few centimeters of the major coronary branches. The finer branches of the coronary tree, coursing within the heart muscle itself, seldom contain occlusive lesions. Because direct surgery to remove obstructions from the coronary arteries has proved risky and the percentage of successes low, surgeons have turned to indirect methods to supplement the blood supply reaching the heart. These methods entail the use of arterial implants or other blood-vessel grafting procedures to connect the heart's intact blood distribution network to a new blood source.

The best known of these procedures involves implanting into the wall of the left ventricle the left internal mammary artery that normally supplies blood to the left side of the chest. The cut end of this artery is inserted into a small tunnel created surgically in the heart muscle. Thereafter, it rapidly forms connecting channels with the heart's collateral

circulation and substantially improves bloodflow to the left ventricle.

Recently, Drs. R. M. Ferlic, F. W. Quattlebaum, and C. W. Lillehei, of the University of Minnesota, developed a procedure that can either supplement the internal mammary implant (for augmenting bloodflow to both ventricles or the anterior and posterior walls of the left ventricle) or else substitute for it when the internal mammary artery is diseased or otherwise unsuitable for implantation. It uses a segment of a vein as an arterial graft. One end of the venous graft is connected end-to-side into the aorta or subclavian artery, the other end inserted into a surgically prepared tunnel in the heart muscle.

The procedure has been used in 37 patients. In 15 of these it was used in combination with internal mammary implants. There were 6 deaths, only 1 of which appeared directly due to the surgical procedure. Followup of the survivors for periods up to 30 months indicate that 30 of the 31 have experienced significant reduction or complete relief of angina and most have been enabled to return to work.

Another technique, devised by Dr. C. W. Pierce and co-workers at Tulane, employs multiple artery implants when severe coronary artery disease has reduced the blood supply to more than one portion of the heart muscle. Their procedure permits implantation of both right and left internal mammary arteries into the anterior and posterior walls of the left ventricle. If necessary, the gastroepiploic artery of the stomach may also be mobilized and implanted into the wall of the right ventricle.

The scientists have employed multiple implants in 22 patients. There was one postoperative death. Nineteen of the 21 survivors have experienced clinical improvement, and X-ray arteriograms have demonstrated that the implanted arteries have remained open and functioning.

The short-term outlook for patients with angina pectoris is definitely improved by propranolol therapy, and internal mammary artery implants may also favorably affect prognosis, according to Drs. S. Wolfson, E. A. Amsterdam, and R. Gorlin, of Peter Bent Brigham Hospital, Boston. Their findings are based on a 2-year review of 135 patients with angina pectoris and coronary artery disease verified by X-ray visualization. Of these, 45 had undergone mammary artery implants and 55 had been treated with propranolol, a drug that selectively blocks receptors through which the sympathetic nervous system affects heart rate and the vigor of heart-muscle contraction. The drug relieves chest pain and improves exercise tolerance in angina patients, presumably by holding heart rate and heart work down to a level commensurate with its reduced blood supply. The control group consisted of 43 patients receiving standard medical therapy, including nitroglycerine and related agents for relief of chest pain.

In the control group there were 6 deaths, 5 heart attacks, and a 56.8 percent incidence of congestive heart failure.

In contrast, among 55 propranolol-treated patients, there was only 1 death, 3 heart attacks, and a 35.8% incidence of congestive heart failure. Among 45 patients who had undergone mammary artery implants to improve the heart's blood supply, there were 3 deaths and 2 heart attacks. In addition, this group had the lowest incidence of congestive heart failure.

Patients with angina pectoris who experience recurrent bouts of chest pain at rest usually have extensive atherosclerosis of the coronary arteries and even slight exertion brings on incapacitating chest pain. However, NHI grantees report on six patients who, despite episodes of chest pain at rest, experienced little or no pain during exertion, a condition they have termed "angina inversa."

When exercised on variable speed treadmills with a 10-degree incline, only two of the six subjects experienced chest pain (after three minutes at 3.5 and 4 mph, respectively). Only one of these exhibited ECG evidence of coronary insufficiency. Two female patients were stopped by fatigue and breathlessness at 2.5 and 3 mph, whereas two other men were able to walk or jog at speeds of 4.5 and 6 mph. Those four neither experienced significant chest pain during the exercise nor exhibited ECG changes indicative of coronary insufficiency.

Drs. R. N. MacAlpine and A. A. Kattus, Jr., of U.C.L.A., report that X-ray visualization of the coronary circulation in these patients revealed a single, well localized obstruction affecting only one major coronary artery and no significant atherosclerosis elsewhere. The scientists reported this distinct clinical syndrome because, when recognized, the underlying focal obstruction can usually be corrected by surgery with good prospects of complete cure.

NHI grantees report the successful use of a CDC 1700 computer to provide a comprehensive record of all arrhythmias occurring in heart-attack patients in a 4-bed intensive coronary care unit. The computer is programmed to scan the electrocardiograms of these patients continuously and instantly recognizes any deviations from normal. The scientists state that the computer provides a rapid, sensitive method for recognizing changes in the patient's clinical state. It also provides complete data on heart rhythm disturbances for correlation with hemodynamic changes occurring in these patients.

These findings were reported by Drs. L. J. Haywood, W. L. Kirk, Jr., G. A. Harvey and D. H. Blankenhorn of the University of Southern California.

The local anesthetic lidocaine appears to be a safe and effective agent for treating and preventing ventricular arrhythmias in patients who have experienced acute heart attacks, according to Drs. R. E. Gianelly, A. P. Spivak, J. van der Groben, and D.C. Harrison, of Stanford.

The heart muscle damage sustained during an acute heart attack makes the heart highly vulnerable to abnormalities in rhythm during the immediate post-attack period. They may reduce the pumping effectiveness of the

heart and also pose the threat of progressing to cardiac arrest. Earlier studies had indicated that lidocaine reduced heart-muscle irritability after open-heart surgery and effectively curbed ventricular arrhythmias developing during the postoperative period.

The NHI grantees used the drug in 21 patients with ventricular arrhythmias following heart attacks. Each received a therapeutic dose of 25-100 mg., then was maintained by intravenous infusions of 0.5-4 mg. per minute for periods up to 72 hours.

Excessive ventricular rates were controlled in 20 instances and the frequency of premature contractions reduced in 17 patients. Therapeutic effectiveness was attained at blood lidocaine levels between 1 and 4 micrograms per cc. No side effects were observed at these levels. Side effects did occur in 2 whose blood levels rose above 8 micrograms per cc. One patient experienced a drop in blood pressure, but it returned to normal when lidocaine was discontinued. The other had two epileptic seizures. He was receiving a very high intravenous dose, having previously experienced recurrent cardiac arrest and brain oxygen deprivation.

The grantees conclude that lidocaine is a safe and effective drug for correcting existing abnormalities in ventricular rhythm and also for preventing their recurrence when given by continuous intravenous infusion.

Clinical studies by NHI grantees underscore the importance of therapy aimed at improving arterial blood pressure as well as heart output in patients with shock resulting from acute heart attacks.

A dreaded complication of heart attacks, cardiogenic shock formerly carried mortality rates ranging from 80-95%. Despite improved therapeutic techniques, it remains a major cause of death in heart attack patients. It appears to stem from the complex interplay of a number of factors: damage to the heart muscle itself, nerve reflexes originating in the autonomic nervous system, hormones from certain endocrine glands, and perhaps others. The salient features are usually failure of the heart to function adequately as a pump and the loss of normal blood vessel tone. The result is often complete circulatory collapse.

One goal of therapy is to increase the amount of blood pumped by the heart. However, the grantees report, this alone is inadequate. Unless there is also an increase in arterial blood pressure sufficient to provide adequate tissue perfusion, blood flow to vital areas is not improved and neither is the patient's clinical status.

Drs. H. S. Loeb, R. J. Pietras, J. R. Tobin, Jr., and R. M. Gunnar, of Cook County Hospital, Chicago, compared the effects of two drugs--norepinephrine and isoproterenol--in 13 patients with cardiogenic shock. Both drugs are powerful heart stimulants; but norepinephrine also acts to raise blood pressure by constricting the smallest arteries (arterioles), whereas isoproterenol dilates them.

Each patient received one, then the other drug. His response to each was

evaluated in terms of average pretreatment values of heart output, arterial and venous blood pressure, and peripheral blood-vessel resistance obtained in 9 of the 13 patients.

Norepinephrine increased heart output by 15% and mean arterial blood pressure by 55%. During the period of increased arterial pressure, the patients' urinary output increased and general clinical condition improved.

Isoproterenol increased heart output by 35%, but arterial pressure fell slightly as a result of a significant decrease in peripheral blood-vessel resistance. No clinical improvement was observed during isoproterenol infusions; in fact, when 4 patients were switched from norepinephrine to isoproterenol, their clinical condition deteriorated markedly within minutes.

Other NHI grantees studied the effects of isoproterenol in patients during the first 3 days of recovery after open heart operations. The drug increased heart output, chiefly by increasing heart rate, and increased coronary bloodflow by an average of 20%. However, this increase did not keep pace with the 27% increase in left ventricular work. Moreover, heart oxygen consumption decreased by 19% as a result of reduced oxygen extraction from the blood presented to it. The sharp rise in heart work coupled with a reduced oxygen supply to heart tissues forced the heart to increase its rate of anaerobic metabolism.

These findings were reported by Drs. H. Mueller, S. Giannelli, Jr., J. J. Gregory, S. M. Ayres, and E. F. Conklin, of St. Vincent's Hospital and Medical Center, New York.

Hypertension

A new drug called Catapres (Geigy) appears to be a potent agent for reducing blood pressure in hypertension. NHI grantees report that oral doses of only 450-900 micrograms a day (a microgram is one millionth of a gram) reduced blood pressure by 20 points or to normotensive levels in 6 of 16 hypertensive patients. When Catapres was supplemented with a thiazide diuretic, similar degrees of blood-pressure control were achieved in 12 of 13 patients. The side effects noted were drowsiness and dryness of the mouth.

Intensive studies were carried out in patients receiving 300-750 micrograms of Catapres. Maximum blood pressure effects occurred after 1-2½ hours, when standing blood pressure fell by an average of 38 points, supine blood pressure by 35 points. The hypotensive effects were accompanied by reductions in heart output, peripheral blood-vessel resistance, and kidney bloodflow.

Catapres, developed in Europe, was intended for use as a nasal decongestant until it was discovered that, on the basis of weight, it was the most powerful hypotensive agent developed to date. The grantees feel that the drug shows promise in the clinical management of ambulatory hypertensive patients.

These findings were reported by Drs. A. N. Brest, K. E. Kim, G. Onesti, J. L. Cangiano, and C. D. Swartz of the Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

A vital role in the regulation of blood pressure is assigned to specialized groups of pressure-sensitive cells called baroreceptors, which continuously monitor blood pressure in various arteries of the cardiovascular system. Perhaps the most important of these baroreceptors is the carotid sinus, located where the carotid artery (to the head) branches in the neck. Somewhat analogous to thermostats in heating or air conditioning systems, the baroreceptors are "preset" to maintain blood pressure within a narrow range. When blood pressure rises above or falls below these values, the barostats detect these changes and attempt to bring blood pressure back within this range. They act through the autonomic nervous system to bring about appropriate alterations in heart rate and output and in blood vessel tone.

There is growing evidence that, with the development of hypertension, the carotid sinus and perhaps other baroreceptors become less sensitive. This amounts to an "upward resetting" of these blood pressure regulators. The reset baroreceptors, regarding elevated blood pressure as "normal," attempt to stabilize blood pressure at excessive levels. Thus they act to sustain the hypertension whatever its original cause.

A novel approach to the treatment of hypertension involves the use of an implantable electronic device to control the activity of the carotid

sinus. The device attempts to compensate for the reduced sensitivity of this baroreceptor by delivering electrical stimuli to the carotid sinus nerves. The device was tested for periods up to 12 months in 12 patients with severe hypertension by Drs. J. Tuckman, T. Reich, A. F. Lyon, and J. H. Jacobson, II, of Mt. Sinai Hospital, New York.

They report that the device effectively slowed heart rate and reduced blood pressure in 8 patients. Two patients did not respond at all to carotid sinus stimulation. In two others the device was initially effective, but lost control of blood pressure 6 and 10 months after implantation. In one of these, adjuvant use of a blood pressure drug restored control; the other patient failed to respond.

The device caused some discomfort in most patients, usually pain in the jaw, throat, inner ear or adjacent regions of the head. The grantees are currently designing and testing different types of electrodes in an attempt to eliminate these side effects.

The stimulus to the upward resetting of the baroreceptors is thought to be frequent or continuous exposure to elevated blood pressure. It is not certain that the resetting is either permanent or irreversible. In fact, there is evidence to suggest that prolonged reduction of blood pressure with drugs may sometimes result in a downward adjustment of the baroreceptors in hypertensive patients, reducing the amount of medication required for blood-pressure control or allowing it to be discontinued altogether for varying periods of time.

Drs. H. P. Dustan, I. H. Page, R. C. Tarazi, and E. D. Frohlich, of the Cleveland Clinic, studied the effects of drug withdrawal in 56 patients previously treated for periods from 1-12 years. Thirty-three patients had essential hypertension, 8 malignant hypertension, and 17 hypertension of renal origin. The periods of non-treatment ranged from 2 weeks to 10 years.

Patient response to discontinuing medication was extremely variable. In 11 patients, blood pressure promptly climbed to or toward previous hypertensive levels within 4 to 6 weeks. In most patients, blood pressure stabilized at levels some 10-15 points above treatment levels or else rose very slowly over a period of 3-27 months. Nevertheless, drug treatment eventually had to be reinstituted in all patients except 2. One, with kidney disease, had remained normotensive for 10 years; the other, with essential hypertension, had been normotensive for 5 years but died of a heart attack.

The results indicated that downward resetting of the baroreceptors often occurs during drug treatment of hypertension, but it is usually temporary. Long-term resetting occurs only infrequently.

Diuretic drugs, which increase salt and water excretion by the kidneys, are used to combat fluid retention in congestive heart failure and other clinical states causing edema. Certain diuretics also reduce blood pressure and potentiate the effects of other antihypertensive drugs.

Previously, the blood pressure effects of diuretics had been attributed primarily to the reduction in circulating plasma volume resulting from drug-induced water losses. However, salt excretion, rather than water excretion, appears to be the key to the blood pressure effects of furosemide and thiazide diuretics, according to Drs. M. Davidov, N. Kakaviatos, and F. A. Finnerty, Jr., of Georgetown and the District of Columbia General Hospital, Washington.

Two to 6 hours after either drug was given intravenously to patients, their blood pressures fell by an average of 16 millimeters of mercury. This was accompanied by a sharp decrease in plasma sodium concentrations and an average reduction of 500 ml (about a pint) in circulating plasma volume.

Maintenance or restoration of normal plasma volume with infusions of Dextran (a plasma substitute) did not affect the hypotensive action of either diuretic. Conversely, infusions of saline, given when the diuretics were administered, did not prevent the drug-induced reduction of plasma volume, but prevented any reduction in blood pressure.

When saline infusions were given after the hypotensive effects of the diuretics had developed, they caused no rise in blood pressure while the drug-induced sodium deficiency persisted. But when positive sodium balance was restored, blood pressure promptly climbed to pretreatment levels.

It has been estimated that 5 to 15 percent of all cases of hypertension may be due to kidney disorders, most often the obstruction of one or both renal arteries by atherosclerosis, clots, or other impediments to normal kidney bloodflow. Reduced bloodflow to the kidney causes it to release renin. In the blood this enzyme gives rise to angiotensin, a powerful blood-vessel constrictor. The renin-angiotensin system is believed to initiate renal hypertension, but whether it is also responsible for maintaining the hypertensive state is not so certain.

Many patients with renal hypertension can be cured or improved by surgery to restore normal kidney bloodflow and/or to remove a heavily damaged kidney. However, a thorough diagnostic workup is essential to select those patients most likely to benefit. Drs. J. H. Foster, R. K. Rhamy, and H. W. Scott, Jr., of Vanderbilt report that two essential tests are 1) X-ray visualization of the renal arteries to reveal and locate sites of obstruction and 2) individual kidney function tests. (In the latter tests urine is collected separately from each kidney by catheters placed in each ureter and/or the renin output of each kidney is determined separately by sampling blood from each renal vein.)

The grantees summarized their operative results in 53 patients. Of these, 28 were cured, 13 improved, and 10 remained unchanged. There were 2 operative deaths. They state that most of the failures occurred in patients whose renal arterial obstructions were corrected even though individual kidney function tests had indicated that these obstructions probably were not responsible for their high blood pressure. In 21 patients subsequently

selected for surgery, primarily on the basis of individual kidney-function test results, 19 were cured or improved. In the two patients that remained unchanged, the operations failed to correct the underlying defect.

Drs. S. Sen, R. R. Smeby, and F. M. Bumpus, of the Cleveland Clinic, have isolated from kidney tissue a phospholipid compound that completely inhibits the blood-vessel response to renin and reduces blood pressure in animals with induced renal hypertension. It has proved effective against the renin of all species tested.

When injected into rats with acute or chronic renal hypertension, 8-15 mg. of the agent per kilogram of body weight reduced blood pressure by as much as 130 points. When injections were discontinued, blood pressures promptly returned to pretreatment levels. The agent had no effect on blood pressure in normal rats.

The agent appears to be a specific inhibitor of renin. It does not prevent the rise in blood pressure normally elicited by infusions of angiotensin. The grantees are currently working out the chemical structure of the agent and seeking to define the nature of its action.

Cerebrovascular Disease

Dr. William B. Kannel and co-workers, of the National Heart Institute's Framingham Study, report that elevated blood hemoglobin, when indicative of an elevated red-blood-cell count, appears to increase susceptibility to stroke resulting from cerebral arterial obstructions.

Moderately elevated hemoglobin appeared to double stroke risk in both men and women. It also appeared to be related to increased risk of high blood pressure, possibly the most serious factor affecting susceptibility to stroke. Among subjects with both elevated hemoglobin and high blood pressure, strokes were 7 times as frequent as among subjects having neither abnormality.

Elevated red-cell counts have been demonstrated to increase heart work, presumably by increasing blood viscosity and resistance to flow through the smallest blood vessels. It may also affect the clotting characteristics of blood. But whether and to what extent these factors affect stroke risk remains to be determined.

Radioisotopic brain scans have proved clinically useful in the detection and localization of brain damage resulting from the blockade of cerebral blood vessels by clots or atherosclerotic deposits (cerebral infarction).

When injected into the cerebral circulation, the radioactive tracer (chloromerodrin labeled with mercury-203) concentrates in damaged brain tissue. When the brain is subsequently scanned by radiation detectors, the "hot spots" resulting from the concentrated radioisotope locate and define the damaged area.

The mechanism whereby the isotope concentrates selectively in damaged brain tissue had not been defined, nor had it been determined why radioisotopic scans were often negative immediately after a stroke, but were positive when the tests were repeated later.

Drs. S. Lunzer, A. W. Dudley, Jr., and A. Heyman, of Duke, studied this problem in animals with surgically induced cerebral infarction. Animals were sacrificed at intervals after the injection of the radioisotope and its localization in their brain tissues was examined. They found that infarcted areas contained 5 to 10 times as much isotope as normal ones; but it was localized, not in the damaged brain cells, but in macrophages. Macrophages are a species of white cell that ingests particulate matter, including bits of dead cells.

Negative brain scans shortly after cerebral infarction with positive scans later on are apparently a function of the time required for macrophages to concentrate in the damaged area.

Congestive Heart Failure

A biochemical defect in the failing heart that may render it incapable of making full use of the chemical energy available to power its contractions has been reported by Dr. B. R. Chandler and co-workers, of the NHI Cardiology Branch.

The immediate source of energy for cardiac contraction is adenosine triphosphate (ATP). Energy generated during the combustion of food-stuffs is stored in the high-energy phosphate bonds of this compound. As needed, this energy is released by enzymes called ATPase. ATPase activity in failing hearts averaged 39% lower than in normal hearts. Since ATPase activity controls the rate of energy release in heart muscle, the observed depression of ATPase activity may underlie the depressed heart-muscle contractility characteristic of congestive failure.

The disease process that often attacks the hearts of chronic alcoholics has been attributed by some to malnutrition, by others to a direct harmful effect of alcohol on the heart. Two studies by NHI grantees indicate that excess alcohol does produce degenerative changes in heart muscle and adversely affects heart function.

Dr. M. B. Bishop and co-workers, of Albany Medical College, fed rats a diet in which alcohol provided 36% of total calories; but the diet contained adequate quantities of protein, vitamins, and other essential nutrients. Nevertheless, after 80 days on this diet, the hearts of the animals were enlarged. Separation of heart muscle fibers and degenerative changes within them were observed under the microscope. Moreover, the heart-muscle fibers from alcoholic rats contracted less rapidly and forcefully than did fibers from control animals and were less responsive to the physiological heart stimulant norepinephrine.

The second study, by Dr. T. J. Regan and co-workers, of the New Jersey College of Medicine, involved alcoholics who had no clinical evidence of heart disease, malnutrition, or nervous system damage. Angiotensin was infused into these subjects and into 6 normal controls. Angiotensin has no direct effect on the heart, but raises blood pressure by constricting blood vessels. The normal heart responds to this blood-pressure rise with more forceful contractions and an increase in stroke volume (the amount of blood ejected per beat).

In the normal controls, stroke volume rose by 25%. In the alcoholics, pressure in the left ventricle at the end of its filling phase rose substantially, but there was no significant increase in the amount of blood subsequently ejected. These findings indicated a significant depression of left ventricular function in the alcoholics.

Subsequently, the alcoholics were studied while consuming alcohol. With increases in the total amount of alcohol consumed, there was a progressive decrease in heart output per beat. Coronary bloodflow did not change, but samples of blood collected after passage through coronary circulation contained increasing amounts of potassium and phosphate ions and of certain heart-muscle enzymes. This suggested that alcohol resulted in the loss of cellular constituents of heart muscle fibers.

Growth retardation in children with congestive heart failure due to congenital heart disease may stem from inadequate insulin according to Drs. G. Hait, A. Gruskin, and E. P. Paulsen, of Albert Einstein College of Medicine, New York. This hormone not only promotes the uptake of glucose by the tissues of the body but also the incorporation of amino acids into protein. The impairment in both carbohydrate and protein metabolism possibly resulting from an inadequate insulin supply may account in part for these children's stunted growth and failure to thrive.

The scientists administered oral glucose loads to three groups of children: 11 normal children; 8 with heart disease but not in congestive heart failure; and 16 with heart disease and congestive failure. Concentrations of glucose and insulin were measured in blood samples collected at regular intervals thereafter. In those heart-disease patients not in congestive failure, glucose uptake and plasma insulin levels did not differ significantly from normal. However, the children in congestive heart failure exhibited delayed glucose uptake and complete suppression of insulin release from the pancreas.

Patients with congestive heart failure frequently have elevated blood levels of norepinephrine and epinephrine. These powerful heart stimulants provide important support to a failing circulation, but they are also known to inhibit insulin release.

Other NHI grantees, studying carbohydrate metabolism in patients with acquired heart disorders resulting in significant reduction of cardiac function, report that such patients show impaired uptake of glucose and abnormally low levels of circulating insulin. This impairment of insulin secretion and glucose uptake was accentuated by infusions of norepinephrine.

Preliminary evidence indicated that, in patients recovering from heart failure, the abnormalities in insulin secretion and glucose uptake diminished as heart function improved.

These findings were reported by Drs. P. D. Ettinger, H. A. Oldewurtel, and T. J. Regan of the Department of Medicine, New Jersey College of Medicine, Jersey City, New Jersey.

A simple, reliable method of ascertaining proper maintenance dosages of digitalis in heart failure patients with impaired kidney function or in patients with altered renal function following surgery has been reported by Drs. R. J. Jelliffe and D. H. Blankenhorn, of the University of Southern California.

The dosage required to maintain body stores of digitalis must balance losses of the drug via kidney excretion. The grantees have found that maintenance doses can readily be calculated on the basis of a simple, routinely performed test of kidney function called the creatinine clearance test. The test is normally employed to measure the rate at which blood plasma is filtered by the kidney, but the grantees found that the rate at which the kidney removes creatinine from the plasma is directly proportional to the rate at which it removes digitalis. Hence, from creatinine clearance rates, which can be determined simply and quickly, the half-life of digitalis can be calculated and the appropriate dosage of the drug determined to hold body stores constant.

In patients whose renal function is expected to change, or in whom improvement or deterioration in function occur in the course of digitalis therapy, repeated creatinine clearance tests permit appropriate adjustments in drug dosage.

Coagulation & Fibrinolysis

Elevated levels of blood clotting factors--sometimes cited as indicative of hypercoagulability--do not of themselves increase the threat of clotting complications of cardiovascular disease. They affect blood coagulability only when present in an activated form, report Drs. S. Wessler and E. Yen, of Washington University, St. Louis. In animal experiments, the scientists studied the effects of activated and non-activated factor X. The activation of factor X is thought to be the first step in the complex sequence of events that lead ultimately to the formation of a clot.

They found that infusions of only 2.5 units of activated factor X produced massive thrombosis in rabbits. When phospholipid, a cofactor in clotting, was added to the activated X, as little as 0.3 units resulted in thrombosis.

In contrast, when non-activated factor X was infused, 650 units did not produce clotting. Phospholipid neither induced clotting alone nor did it cause non-activated factor X to do so.

Thus it appears that whereas clotting factor deficiencies can induce bleeding tendencies. clotting factor elevations do not result in hypercoagulability, so long as they are not activated.

Heparin, an anticoagulant added to the blood used to prime heart-lung machines, reduces the threat of clotting complications during open-heart surgery. However, after the operation, it must be neutralized to prevent excessive blood loss during the healing period. Heparin is readily neutralized by a compound called protamine sulfate; but this heparin antagonist can itself produce a bleeding tendency if given in excessive amounts

Dr. K. Ramaswamy and co-workers, of Tufts University, Boston, report the results of their studies indicating that the recommended dosage of protamine is, in fact, excessive and may be responsible for some instances of hemorrhage occurring after open-heart procedures.

The two groups of patients studied were similar with respect to clinical status and the amount of heparin received in conjunction with heart-lung bypass. However, postoperatively, one group (33 patients) received the recommended dosage of protamine sulfate (1.02 mg. per 100 U.S.P. units of heparin), whereas in the other group (32 patients), the protamine dosage was reduced to 0.62 mg. per 100 units.

The reduced protamine dosage normalized blood clotting times within 25 minutes. Blood loss through the chest tubes ceased within 24 hours in 19 of the 32 patients and total blood drainage averaged only about 17 cc. per kilo of body weight.

In the 33 patients receiving the recommended protamine dosage, blood loss through the chest tubes had ceased in only 8 patients after 24 hours and total blood drainage averaged 29 cc/kg. Five patients required exploratory surgery for excessive bleeding and one of these died. In all 5, diffuse

oozing rather than hemorrhage from some specific site was found to be the cause of blood loss. The grantees conclude that a protamine-induced bleeding tendency was probably responsible for the poorer results obtained in this group.

NHI grantees report that reflected ultrasound provides a rapid, sensitive, and safe diagnostic test for pulmonary embolism, the blockade of pulmonary blood vessels by blood clots.

Pulmonary embolism is a fairly common, frequently serious complication of inflammatory disease of the veins (thrombophlebitis), and it also poses a threat in any patient who must be immobilized for prolonged periods. Clots, usually arising in the deep veins of the legs, may break free, be carried to the right heart, then pumped to the lungs, where they become lodged in smaller arteries of the pulmonary circulation. The disorder is not easily diagnosed or its seriousness readily evaluated on the basis of clinical findings alone. Thus scientists have sought safe and reliable tests to determine the site and extent of arterial blockade as a guide to clinical management and to evaluate the effectiveness of therapy.

Two techniques are currently in clinical use. One entails injecting radiopaque contrast material into the pulmonary artery, then following its course through the pulmonary circulation with rapid-sequence x-rays to locate sites of blood-vessel obstruction. The other involves introducing albumin tagged with radioactive iodine, then scanning the lungs with a suitable radiation detector. Blood-vessel obstructions prevent the labeled albumin from reaching the portions of the lung supplied by those vessels, creating "cold spots" in the lung scan. Although both of these are effective diagnostic tests, neither is simple to perform and neither is completely without hazard to a critically ill patient.

The NHI grantees have found that ultrasound, beamed into the chest by a transmitter placed on the patient's chest, produces a distinct pattern of echoes from sections of the lung deprived of blood by arterial blockade. Such "pulmonary echograms" were obtained from 218 patients. Echograms indicative of pulmonary embolism were obtained in 65.

In 11 of these patients, the accuracy of the pulmonary echogram was confirmed by subsequent surgery or at autopsy. Thirty-six others also had radioisotopic lung scans and 2 others pulmonary x-ray arteriograms. In 36, these tests confirmed the diagnosis, and the findings correlated closely with those of the echograms. One patient with a positive echogram but a negative lung scan proved, on autopsy, to have pulmonary embolism.

The scientists found that echograms suggestive of pulmonary embolism may occasionally be produced by other lung disorders, such as lobar pneumonia, a collapsed lung, or cancer; but state that "false positive" diagnoses are unlikely if echograms are correlated with other clinical and radiological findings. They conclude that the pulmonary echogram is a rapid, simple, and safe diagnostic technique whose accuracy and sensitivity appears equal or superior to radioisotopic lung scans.

These findings were reported by Drs. C. R. Joyner, J.W. Gruber, S.J. Dudrick, and L. D. Miller, Robinette Foundation, Department of Medicine, and the Harrison Department of Surgical Research, University of Pennsylvania, Philadelphia, Pa.

Patients with pulmonary embolism stand to benefit from urokinase therapy if their symptoms have not been present for more than 2 weeks, according to Drs. E. Genton and P. S. Wolf, of the University of Colorado.

Urokinase is a drug that brings about the dissolution of blood clots by activating the body's normal clot-dissolving mechanisms. The "fresher" the blood clot, the more susceptible it is to dissolution. Earlier animal studies had indicated that urokinase could achieve near-complete dissolution of clots 7 days old and partial dissolution of 14-day-old clots. Clots older than this were resistant to attack by the drug.

Urokinase has subsequently been tested in 10 patients with pulmonary embolism documented by x-ray arteriography.

In 3 patients, symptoms had occurred within 2 weeks of urokinase therapy. All patients exhibited marked relief of symptoms, improvement of lung function, and arteriographic evidence of clot dissolution.

Three patients had experienced symptoms for more than 2 weeks, but also had evidence of fresh embolism superimposed on their pre-existing condition. In these patients urokinase therapy produced some relief of symptoms, but lung function improved only slightly.

Three other patients had histories indicative of months to years of recurring pulmonary embolism and only slight worsening of symptoms within 2 weeks of urokinase therapy. In these patients, therapy produced no detectable improvement. The tenth patient had acute symptoms, but these proved to be due to an old, organized clot. The patient, in shock when urokinase was administered, showed no improvement and subsequently died.

The clinical results supported the findings of the earlier animal studies: urokinase accelerates the dissolution of fresh clots, but not of "old" ones.

Surgery

Limited clinical experience by NHI grantees indicates that pulmonary artery and pulmonic valve malformations in patients with tetralogy of Fallot can be surgically corrected with healthy aortic and aortic-valve homografts obtained from human donors dying of causes other than cardiovascular disease.

Tetralogy of Fallot, a major cause of "blue babies," is a complex of congenital heart abnormalities. These include 1) a hole, usually large, in the muscular wall between the left and right ventricles; 2) displacement of the aorta to the right, so that it receives blood from both ventricles; 3) narrowing of the portion of the right ventricle lying just below the pulmonic valve and/or malformation of the pulmonic valve itself; and 4) enlargement of the right ventricle. The overall result of this combination of defects is reduced bloodflow to the lungs and the mixing of large

quantities of oxygen-poor venous blood with oxygenated blood destined for the organs and tissues of the body.

In the surgical correction of tetralogy of Fallot, pulmonic valvular malformations have proved least amenable to repair. Forcibly dilating a narrowed pulmonic valve may relieve the obstruction to pulmonary artery bloodflow, but often leaves the valve incompetent, so that it allows regurgitant flow. Replacement of the pulmonic valve with an artificial valve has not been feasible because of excessive risk of clotting complications.

Clinical experience with aortic valve homografts have shown them to be singularly free of clotting complications when used to replace diseased aortic valves. Accordingly, Drs. C. S. Weldon, R. D. Rowe, and V. L. Gott, of Johns Hopkins, used them as substitutes for deformed or congenitally absent pulmonic valves in 3 patients undergoing surgical correction of tetralogy of Fallot. All three also had pulmonary artery malformations which were corrected with aortic homografts.

One patient, who had done well for 3 months after surgery, subsequently developed bacterial endocarditis and died. The other 2 patients had uncomplicated recoveries.

A common complication of bacterial infections attacking the inner lining of the heart is heavy damage to the aortic valve. The malfunctioning valve may bring on acute heart failure, which is the most common cause of death in bacterial endocarditis. Drs. B. A. Braniff, N. E. Shumway, and D. C. Harrison, of Stanford, report that, if aortic valve incompetence precipitates heart failure that does not respond to medical treatment, valve replacement should be done whether or not the bacterial infection is under control.

The surgeons carried out valve replacements in 5 patients with life-threatening congestive heart failure developing during bacterial endocarditis. All had active endocarditis and only one had completed his antibiotic regimen. Surgery promptly reversed progressive heart failure in all 5, and no patient developed evidence of infection or heart failure during the recovery period. All patients were alive and well 7 to 28 months after surgery.

The addition of glucose, insulin, and potassium to the blood and Ringer-lactate solution commonly used to prime the heart-lung machine may minimize adverse effects of prolonged heart-lung bypass in conjunction with open-heart surgery, according to Drs. A. L. Davies, M. J. Buckley, and W. G. Austen, of Massachusetts General Hospital. This "enriched" prime was tested in 15 dogs, each undergoing 2 hours of heart-lung bypass. All animals survived in good clinical condition. There was little postoperative depression of heart and nervous-system function and only minimal changes in blood acid-base balance.

Ten control animals underwent the same period of heart-lung bypass using the conventional prime of blood and Ringer-lactate solution. Two died during bypass. Four survivors had moderate depression of heart function. All survivors exhibited marked abnormalities in blood acid-base balance and depression of the central nervous system.

The grantees are currently investigating the nature of the protection conferred by the glucose-insulin-potassium supplement. They suspect that it helps to maintain the integrity of cellular membranes of the heart and other tissues and thus prevents potentially harmful losses of essential electrolytes by the cells.

NHI grantees report that there is no adequate substitute for blood-volume determinations to insure restoration of normal blood volume after open-heart operations. Neither measurements of blood loss during surgery nor of central venous pressure provide sufficiently reliable guides to blood replacement therapy.

Blood volume determinations were run on 100 consecutive surgical patients as a check on the adequacy of blood replacement. The tests revealed an average deficit of 12.6 percent in 26 patients whose measured blood losses had been replaced 1.4 fold. Of 74 patients in whom replacement therapy was based on measurements of control venous pressure, near normal blood volumes were achieved in 32, but deficits ranging from 10-31 percent were detected in 22 patients. Correction of the deficits substantially improved heart performance.

Blood volume determinations are simple to perform. By one method, a measured quantity of radioactive iodine is injected and allowed enough time to become evenly distributed in the blood. A measured quantity of blood is then withdrawn and its radioactivity measured to determine the extent of dilution of the tracer. From this, the blood volume is easily calculated.

The grantees state that routine blood-volume determinations make possible accurate restoration of pre-operative blood volume, avoiding blood deficits and also overtransfusion, with its attendant threat of congestive heart failure developing during the postoperative period.

The findings were reported by Drs. R. L. Berger, M. L. Polanzak, and T. J. Ryan of St. Elizabeth's Hospital and Tufts University School of Medicine, Boston, Massachusetts.

Drs. J. M. Matloff and co-workers, of Peter Bent Brigham Hospital, Boston, report that the drug propranolol provides excellent control of post-surgical atrial arrhythmias that have failed to respond to countershock or digitalis therapy.

Efficient contraction of the heart's upper receiving chambers, or atria, aids the filling of the ventricles and thus contributes importantly to overall heart pumping performance. Atrial arrhythmias upset the smooth contraction sequence of these chambers and impede delivery of blood to the ventricles. Runaway rates of atrial contraction (atrial tachycardia) or the spasmotic, ineffectual contractions of atrial fibrillation are often accompanied by extremely rapid ventricular rates. The combination can so severely compromise heart performance that the patient may develop con-

gestive heart failure or serious symptoms of coronary or cerebral insufficiency.

Propranolol is a drug that selectively blocks beta receptors of the sympathetic nervous system, which exerts a considerable degree of control over heart rate and rhythmicity. Stimulation of beta receptors increases the firing rate of the heart's pacemaker (the sino-atrial node located in the upper right quadrant of the right atrium) and also affects the heart-muscle response to pacing stimuli. Blockade of beta receptors with propranolol slows the pacemaker, curbs runaway atrial and ventricular rates, and restores the normally smooth contraction sequence of the heart chambers.

The grantees used the drug in 22 patients developing refractory atrial arrhythmias after cardiac surgery. These arrhythmias had failed to respond to countershock, digitalis, or quinidine. Propranolol effectively slowed the high ventricular rates in all patients and restored normal heart rhythm in 15. The scientists conclude that propranolol, carefully used, is an extremely valuable drug for managing post-surgical atrial arrhythmias that resist conventional methods of treatment.

Congenital heart defects causing severe tissue oxygen deficiencies often result in a sharp increase in red-blood cell production. Whether this "compensatory polycythemia" is good or bad for the patient has been a matter of some controversy. An elevated red-cell count does increase the oxygen-carrying capacity of the blood; but it also increases the viscosity of the blood, making it harder for the heart to pump and increasing its resistance to flow in the smallest blood vessels.

Dr. R. L. Replogle and co-workers, of the University of Chicago Medical School, studied this problem in normal dogs and in dogs with blood-oxygen deficiencies resulting from surgically induced heart defects to interfere with bloodflow to the lungs. Red blood cell count was increased by removing a quantity of whole blood then replacing it with a concentrated red-cell suspension.

In both groups of dogs, the red-cell infusions reduced heart output from an average of 1430 ml. per minute to only 546. Blood viscosity and resistance to flow increased markedly. The overall result was a substantial decrease in the amount of oxygen reaching the tissues.

The grantees conclude that even moderate increases in red-cell count can markedly alter the flow properties of blood and produce profound circulatory and metabolic consequences. In view of the consequences noted in this study, it would appear that "compensatory polycythemia" in patients with congenital heart disease and cyanosis is more likely to worsen the tissue oxygen deficiencies than to ameliorate them.

Complex congenital heart malformations often cannot be surgically corrected during infancy. Instead, a palliative operation may be performed to keep the infant alive and reasonably healthy until he is older, when corrective surgery is less risky and more likely to succeed. A palliative procedure often employed in infants with tetralogy of Fallot or other congenital defects resulting in decreased bloodflow to the lungs is the Blalock-Taussig operation. It entails directing bloodflow from a major systemic artery (the left subclavian) into the pulmonary circulation. The left subclavian artery is severed near its point of origin, the aortic arch. The proximal portion (closest to the aortic arch) is then spliced, end-to-side, into the pulmonary artery; the other segment is tied off. The tied off segment includes a small subclavian branch, the left vertebral artery, which normally supplies some blood to the brain.

Drs. R. I. Tapper, J. S. Vasko, and J. W. Kilman, of Ohio State, had observed that, even though this operation spares the major arteries to the brain, a significant number of patients developed postoperative symptoms, usually transient, of cerebrovascular insufficiency. To determine the cause of these symptoms, they performed Blalock-Taussig operations in dogs, then studied resultant bloodflow in the arteries supplying the brain.

Feeding a large, high-pressure systemic artery into the low-pressure pulmonary circulation reduced the resistance against which the left ventricle worked in pumping blood and increased its output by about 28%. However, it also reduced the perfusion pressure of the vessels to the brain arising off the aortic arch. As a result, despite the increased heart output, there were substantial decreases in average bloodflow through the carotid arteries and the right vertebral artery. These reductions were due chiefly to substantial backflow of blood in these arteries occurring between pumping strokes.

Another factor was the left vertebral artery arising from the tied off section of the left subclavian. Bloodflow in this vessel was reversed, and the resulting blood loss to the brain averaged 50% of that reaching it through the right vertebral artery. The grantees state that this "subclavian steal" phenomenon, which might underlie symptoms of cerebral insufficiency, was eliminated by tying off the left vertebral artery.

Other NHI grantees report that the "subclavian steal" phenomenon may have been responsible for some of the failures incurred in operations requiring complete replacement of the aortic arch because of extensive aneurysms affecting that segment.

Despite success in replacing the diseased aortic segment and in re-establishing connections between the graft and arteries arising from the aortic arch, the overall operative results had been disappointing. The chief cause of failure was brain damage, apparently resulting from inadequate perfusion during surgery.

During the procedure the surgeons had clamped both subclavian arteries upstream from the vertebral arteries and had perfused the brain only via the carotid arteries. They think it likely that backward flow in the vertebral arteries downstream from the clamps may have been robbing the brain of blood. In two subsequent operations, they supplemented carotid perfusion with retrograde perfusion of the clamped subclavian and its vertebral branch (via the axillary artery). They state that this eliminated cerebral complications of aortic arch replacement.

These findings were reported by Drs. R. D. Bloodwell, D. A. Cooley, and G. L. Hallman of the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, Houston, Texas.

All heart-lung machines of current design cause some damage to red-blood cells. This damage may result in breakdown of these cells (hemolysis) or it may shorten their survival in the circulation. Studying this problem, NHI grantees found that most of the damage stemmed, not from mechanical trauma incurred during passage through the blood pump, but from interaction with the chemical substance (polymethylsiloxane) used as a defoaming agent. The chief cause of foaming is aspiration of blood from the operative site to prevent it from obscuring essential anatomical details during surgery. This is removed in a defoaming chamber before the blood re-enters the patient's circulation. Drs. R. Wells, S. Bugdeman, and A. A. Wells, of Peter Bent Brigham Hospital and Harvard Medical School, subsequently found that blood cell damage resulting from contact with the defoaming agent could be prevented by Pluronic, an agent used to prevent fat emboli in heart-lung machines. Pluronic did not interfere with the defoaming action of polymethylsiloxane. In fact, the grantees state, certain Pluronic derivatives have defoaming actions of their own.

Bioengineering

Complete heart block usually results from disease or operative injury to the specialized conduction system that normally initiates and conveys to all parts of the heart muscle the electrical impulses causing heartbeat. Heart block may slow heart rate and decrease its output of blood below the level required to sustain normal activity, and it poses an ever present threat of arrhythmias that may progress to heart stoppage and death.

Normal heart rate may be restored and maintained in heart block patients by any of a number of currently available artificial pacemakers. These electronic devices may deliver their pacing pulses to the heart either by wire electrodes implanted in the heart muscle wall via an incision in the chest (transthoracic pacing) or else the electrodes may be introduced into the right ventricle by a catheter, usually passed into the heart via the jugular vein (transvenous pacing).

Dr. J. W. Harthorne and co-workers, of Massachusetts General Hospital, report that transvenous pacing is attended by fewer complications and yields better long-term results than does transthoracic pacing.

Transvenous pacing was used in 56 of the 100 cases in this series. No complications were encountered during electrode implantation. There were 5 late deaths, none of them due to pacemaker failure. In the 51 survivors, 6 pacemaker problems have occurred during follow-up periods averaging 9 months. Five of these were easily corrected; the sixth required switching the patient from transvenous to transthoracic pacing.

Transthoracic pacing was used in 44 patients. Four patients failed to recover from the major surgery required for electrode placement. There were 6 late deaths, only one of which appeared due to pacemaker failure. However 25 of the 34 long-term survivors have experienced a total of 52 pacemaker problems. A major problem has been electrode breakage, apparently the result of the greater stresses imposed on transthoracic electrodes by the incessant motion of the heart. Five patients were subsequently switched from transthoracic to transvenous pacing.

The grantees conclude that, although transthoracic pacing can provide satisfactory control of heart block, the transvenous approach, being both simpler and safer, is clearly the procedure of choice.

Drs. C. A. Hufnagel, P. W. Conrad, and R. R. Schulte, of Georgetown, have developed a new artificial aortic valve that combines strength, durability, and excellent performance characteristics in a design that is anatomically very similar to the normal aortic valve.

The three leaflets of the valve, which are suspended from three vertical posts arising from the base ring, consist of a thin layer of tough, resilient polypropylene mesh embedded in soft rubbery silicone. They are designed for a flex life exceeding human life expectancy. They open under very low pressure to provide a maximum orifice during forward bloodflow, but close firmly and completely at the end of the ventricular pumping stroke to prevent backflow. The base ring configuration is specifically designed to fit the aortic annulus, the ring of tissue remaining after excision of the aortic valve and to which the replacement valve is anchored. To prevent clotting on valve surfaces, the silicone coating of the base ring, valve leaflets, and supporting posts are specially treated to incorporate heparin, an anticoagulant.

The valve has been installed in nine patients. All survived and had an unusually smooth postoperative course. All have exhibited excellent postoperative valve function.

NHI grantees report the development of a miniaturized electromagnetic flowmeter probe that can be mounted in the tip of a catheter only 3.3 mm. in diameter. The flowmeter probe generates a magnetic field. When blood, a conductor of electricity, flows by the probe it cuts across the surrounding magnetic lines of force and induces a voltage in the probe that is proportional to the velocity of flow.

The grantees tested the flowmeter in the aortas of dogs, comparing the results with those obtained with a conventional perivascular flowmeter

that must be implanted around the blood vessel in which flow is monitored. The measurements obtained with the catheter tip flowmeter were in good agreement with those obtained with the perivascular flowmeter, both at high and low flow rates.

The advantages of the new device are that it does not require surgical exposure of blood vessels to measure flow within them and can be freely maneuvered along the length of the vessel rather than measuring flow only at a single site.

A new heart assist device has performed well in limited clinical trials conducted by Drs. W. S. Blakemore, E. T. Tragus, C. L. Arnstadt, and A. E. Baue, of the University of Pennsylvania. The device has a glass outer housing that is placed around the heart. The housing contains an elastic diaphragm that fits snugly around both heart pumping chambers.

Compressed air, forced into the housing, causes the diaphragm to squeeze down on both ventricles, thus assisting them in expelling blood. Subsequently, the air is sucked out, pulling the elastic diaphragm back from the ventricles and allowing them to refill.

Previous studies had established that the device could maintain a normal heart output and blood pressure in animals despite induced fibrillation (spasmotic, uncoordinated heart contractions). Subsequently it was tested in three patients. In two, the device sustained the circulation for two hours and could have sustained it longer had there been hope for recovery. The third patient had severe fibrillation that had not responded to heart massage or countershock. The device sustained his circulation for 41 minutes, after which defibrillation was successful and the patient survived.

Highlights of Research Progress
during 1967

from

National Institute of Dental Research

## Caries

Caries is the process of dental decay which begins with chemical changes in enamel and dentin, continues through erosion, and the formation of cavities to the painful destruction of the tooth. Interactions between bacterial, dietary, and hereditary factors account for most caries.

Test permits large-scale surveys.--Several types of bacteria, particularly various streptococci, are associated with dental decay. Because every mouth harbors myriads of bacteria which look much alike, and because many of these organisms die quickly when removed from the mouth, it has been virtually impossible heretofore to study the distribution of caries-causing bacteria in various populations. To relate the numbers of bacteria in the mouth to the degree of decay, the number of other bacteria, or the amount of plaque present has been equally difficult.

Now B. Krasse and A. Möller of Sweden, collaborating with H. V. Jordan of the Dental Institute, have developed a method in which plaque, a sticky film, can be scraped from teeth and put into a special transport medium which will preserve the plaque-associated bacteria alive for about a week at room temperature. During this interval, the samples can be shipped to a central laboratory. Once there, measured amounts of plaque are mechanically dispersed, spread over an agar-gel growth medium, and incubated under a mixture of carbon dioxide and nitrogen gases. This treatment enables known caries-forming bacteria to grow into easily recognizable colonies. Also, their numbers in proportion to those of other bacteria in the plaque can be counted. Now for the first time, large-scale studies can be made. Surveys can be undertaken to find out whether the bacteria that cause rampant caries in the United States are the same as those in other parts of the world. It can be determined whether or not most people have these bacteria; and, if they do, approximately how many must be present for decay to develop.

Bacterial polysaccharide.--Strains of bacteria known to cause decay can, particularly in the presence of sugar (sucrose), produce large amounts of a sticky polysaccharide material which surrounds them in a jelly-like substance. Bacteria which do not cause decay never produce more than a trace of this material. Institute-supported

research at Forsyth Dental Center shows that maximum bacterial growth of certain of these decay-causers takes place when there is two percent of sucrose in the broth medium. The amount of the polysaccharide increases with the amount of sucrose up to a maximum of ten percent. But even when growing in a less favorable 15 percent sucrose solution, one of these bacteria can, in terms of dry weight, produce 70 times its own weight in polysaccharide. Other sugars such as glucose and maltose will also permit these bacteria to make polysaccharide. Chemical and immunological tests of this material show that it is a dextran which binds to the tooth mineral, and in the presence of saliva forms an insoluble precipitate comprising 1.8 percent of the dry weight of dental plaque. R. J. Gibbons and S. B. Banghart of the Forsyth Dental Center and Harvard University give evidence that this substance is the basis of plaque formation, and plaque supplies the framework for most decay-causing activity.

Locus of decay.--Studies employing antibiotics and various diets in rats have shown that bacteria which cause decay in the pits and fissures of teeth apparently differ from those which damage smooth surfaces. A variety of diets enable the smooth-surface attackers to survive, but decay occurs only when conditions are especially favorable. According to R. H. Larson and others of the Dental Institute, the rats must eat food which not only permits bacteria to produce plaque, but is smooth enough not to scrape the plaque off, and contains a high percentage of fermentable sugar. Therefore, some diets promote caries on all surfaces, whereas others support decay only in pits and fissures. Here bacteria are largely protected from mechanical scraping, and food particles are more easily trapped for considerable periods of time.

Plastic coat protects tooth.--One possible method of preventing decay in high-risk children has been reported by E. Cueto and H. Buonocore at the Eastman Dental Center in Rochester, New York. These investigators clean the teeth, pretreat the enamel to prepare it for an adhesive, and then cover the pits and fissures in the grinding surfaces with a plastic mixed with fine silica particles. In this way areas least protected by fluoride, and highly susceptible to decay are sealed off from mouth fluids. The adhesive wears off in time, but gives excellent protection for six months. Even after a year, 86 percent fewer cavities appeared in treated teeth than in untreated ones in the same mouths.

Because older people tend to have fewer cavities, it may be that preventing decay in high-risk children for a few crucial years will allow them to pass safely through the danger period. This procedure has not yet been sufficiently evaluated to be recommended for general use.

Screen antibiotics in animals.--It has often been suggested that caries and other mouth diseases could be reduced with antibiotics. However, the likelihood of allergic reactions to these

drugs and of gradual development of drug-resistant organisms has necessitated a cautious approach to this method.

NIDR scientists report that hamsters are suitable for testing various drugs against tooth decay and periodontal (gum) diseases. These ailments can always be produced in a short time if the young animals, fed a high-sugar diet, are infected with certain streptococci or filamentous microorganisms. Moreover, the teeth, including molars, are easy to see in hamsters. Once disease is established, drugs can be added to the diet or applied to the teeth. Then it is easy to compare the efficacy of various drugs or treatments in checking or reversing the course of disease.

P. H. Keyes and others report that of various antibiotics tested only two proved helpful. Vancomycin hydrochloride, which is sometimes injected into veins to treat human staphylococcal infections, retarded but did not stop tooth decay when it was simultaneously applied to teeth and included in the diet. However, it did control gum disease. Spiramycin, whether incorporated in food or painted on teeth, controlled both diseases so long as regular treatment lasted, but disease returned when the antibiotic was discontinued.

Decay-supporting foods.--An NIDR study by R. M. Stephan has focused on patients with rampant caries. These people, in general, were found to eat only one or two regular meals a day. The rest of the time they nibbled frequently on a selection of favorite foods. Fifty-three varieties of these foods were fed to rats to see what effects each by itself had on plaque formation, dental erosion, calculus (tartar) formation, caries, and bone structure.

A few items: whole milk, popcorn, peanuts, and dog biscuit (eaten by some children) seemed to reduce decay. Another group of foods, including lettuce, cabbage, and corn chips, had no effect on decay. Acid fruits, lemons, oranges, and dried apricots produced some erosion but no decay. A slight increase in decay was attrubutable to soda crackers, cracked-wheat bread, and potato chips, while moderate decay was associated with whole-wheat bread, raisin bread, graham crackers, carrots, cornstarch, and white bread whether alone or with butter, peanut butter, or as melba toast.

Finally, all the significantly cariogenic foods tested contained considerable amounts of fermentable carbohydrates. In this group are many sugars and sugar-containing fruits, cookies, candies, and soft drinks. Sucrose caused the most decay. Foods which stick to and between the teeth generally increased decay more than those which did not remain long in the mouth. It is interesting that milk sugar (maltose) was relatively non-cariogenic, and whole milk caused no decay. If more foods could be identified as harmless to teeth and provided commercially in snack form to compulsive nibblers who are highly susceptible to decay, rampant caries might be considerably reduced.

Food, acidity, plaque related.--Acidity is perhaps the chief decay-causing factor in plaque and is attributed to the fermentation of carbohydrates by mouth bacteria. The bacteria and the acid are held by the plaque close to the tooth. A study of the relationship between food, acidity, plaque and caries was carried out by N. W. Littleton of the National Institute of Dental Research and other scientists on a group of severely handicapped and retarded patients. These people have some dental plaque and calculus regardless of the way they are fed, but those who are fed by stomach tube develop less plaque than those fed by mouth. The investigators wondered whether the absence of food particles might reduce the accumulation of acid produced within plaque by bacterial fermentation. They found that when plaque was removed from tube-fed patients and mixed with a sugar solution, the increase in acidity after 30 minutes was five or six times less than that in plaque taken from mouth-fed patients and treated the same way. Whenever the method of feeding had to be changed, whether from tube to mouth or vice-versa, within a relatively short period of time the acid potential within plaque reversed accordingly.

Diet factor complex.--Some of the interactions between decay, bacteria, and diet are exceedingly complex. An Institute scientist, R. H. Larson, reports that when the principal parts of a standard caries-inducing diet in rats are kept practically uniform, small changes in the salts and diet supplements, such as yeast and liver powder, can make a great difference in the amount of caries the animals will develop. In fact an inbred, caries-resistant strain will develop more decay than another inbred susceptible strain, because the new, slightly varied diet supports bacterial activity which was not possible before.

## Fluoride and Bone Studies

Evaluate types of fluoride.--So far the most effective preventive agent against tooth decay is fluoride, which, when it combines with tooth mineral to form fluorapatite, makes teeth much more resistant to caries. In places where there is little fluoride in the water, extra fluoride is often provided to teeth by topical applications of either stannous or sodium fluoride. Seeking to explain the varying degrees of protection provided by the different salts, F. Brudevold and others at the Forsyth Dental Center, Harvard University, have shown that if certain substances are present which react with the fluoride salts to form insoluble precipitates, they can reduce the amount of fluoride available to form fluorapatite. This sort of interference can come from chemicals in mouth fluids, from incompatible abrasives in tooth paste, or from other substances in various solutions of fluoride used as mouth washes or topical applications to treat teeth.

Hypothesizing that insoluble precipitates might lessen fluoride availability, these scientists report that the amount of fluoride

taken up by tooth enamel decreases as the percentage of tin in stannous fluoride solutions increases. Other research, however, has reported good protection with stannous fluoride. Institute investigators emphasize that the best form of fluoride has not yet been conclusively demonstrated, and the main emphasis at this time should be upon more widespread use of one accepted form or another of this invaluable protective substance.

Fluoride gel studies extended.--Field trials of applying fluoride by means of gel-coated, plastic mouthpieces have been extended to determine, for example, (1) whether the initial success in preventing decay in Cheektowaga, New York, will be maintained in other populations, (2) whether the use of the gel technique in an area where water is fluoridated adds to the decay prevention, and (3) whether use of the gel by preschool children provides a foundation for defense that will be maintained later.

In the gel technique, reduction in caries is achieved when an individual places in his mouth, for a few minutes a day, a custom-made, fluoride-gel-coated mouthpiece. The fluoride thus is held close against the teeth and is protected by the mouthpiece from dilution with saliva. In schoolchildren of Cheektowaga the reduction in decay, reported last year, was approximately 80 percent. Drinking water is not fluoridated in Cheektowaga. The study of the gel technique now has been extended to Charlotte, North Carolina, schoolchildren and to preschool-age children of Coast Guard families at Governor's Island, New York. In both of these areas the water supplies are fluoridated.

An initial test of teeth lost naturally by study youngsters in Charlotte shows that the high levels of topically-applied fluoride are getting into defensive position in the enamel, but results from this study and that at Governor's Island will not be available for a number of months.

In the course of the first fluoride gel study, the children shed 86 primary teeth which have now been analyzed to show the amount of fluoride present at different depths in the enamel after each type of treatment. Because fluoride is always more concentrated in the outer layers of enamel, it is important to be able to increase not only the amount of fluoride but the depth of the zone of concentrated fluoride if resistance to decay is to be increased.

When four successive layers of enamel of comparable thickness were dissolved in acid and tested for the amount of fluoride present in the solution, it was evident that all four layers from teeth treated with acid-phosphate sodium fluoride had more fluoride than comparable layers from teeth treated with neutral sodium fluoride, and much more than untreated teeth. Fifteen applications of acidulated gel produced the same concentration of surface fluoride as 74 applications of neutral gel. Not only did the outermost layer

(about ten microns thick) of teeth treated with acidulated phosphate gel have 37 percent more fluoride than the same layer of those treated with neutral gel, but the second, third, and fourth layers, down to depths of over 50 microns, had respectively 78, 35, and 80 percent more fluoride.

Because the fluoride in the deeper layers increases steadily with the number of applications of acidulated phosphate gel, whereas the effect of neutral gel is relatively small on comparable inner layers, J. Mellberg and C. Nicholson of Kendall Research Laboratories, Barrington, Illinois, and H. Englander of the National Institute of Dental Research consider that phosphate-acid reactions help the fluoride to diffuse deeper into teeth before it combines with the enamel crystals.

Calcification and Bone Studies

Fluoride and bone composition.--A bone study by I. Zipkin and P. D. Frazier of the Dental Institute shows the effects of fluoride on two different inbred strains of mice. Thigh, knee, and pelvic bones were compared chemically and by X-ray diffraction when both mouse strains were given drinking water with and without fluoride. One strain is large-boned, heavy, and develops osteoarthritis by the time it is 16 months old. The other strain is small-boned, lighter, and does not develop arthritis. When both strains drink distilled water and live under the same conditions for 15 months, the heavy strain has seven percent more ash, 31 percent more citrate, and 20 percent more carbonate in its bones than the light one. These hereditary chemical differences were previously unknown. When both strains drink highly fluoridated water for 15 months but otherwise follow the previous regimen, the heavy strain still has higher percentages of ash, citrate, and carbonate, plus more fluoride, than the light one. However, both strains have lower levels of citrate and carbonate, and higher levels of ash than animals not on fluoride.

This research shows that fluoride alters the chemical composition of bone. The X-ray diffraction studies also show improved crystallinity in the bone structure of the animals which drink fluoride. However, fluoride does not affect the development of arthritis in the heavy mice.

Some scientists have thought that the action of fluoride is primarily local, and that topical application to prevent tooth decay is all that is necessary. However, today there is accumulating evidence that systemic fluoride improves bone as well as teeth, thereby extending benefits far beyond the mouth.

Amorphous phase in teeth.--Problems of tooth loss continually lead to studies of bone, cementum, dentin, and enamel in the hope of learning how to check decalcification and encourage recalcification. Recent X-ray diffraction, infrared spectroscopic, and

electron spin resonance studies by J. D. Termine and A. S. Posner of Cornell University Medical College, indicate that the mineral portion of bone and dentin, formerly thought to be composed entirely of submicroscopic crystals of calcium phosphate, is not so simple. Apparently, a more chemically reactive amorphous phase of calcium phosphate usually precedes the formation of the crystalline phase in the test tube. In animals both phases occur together in bone and dentin. There is more of the amorphous phase in all types of young bone in all species studied from human to chick. The amorphous phase may account for the greater adaptability and some of the flexibility of young bones. As bones mature with age, the crystalline phase gradually increases and finally predominates.

Etiology of pulp stones.--In the course of a study of the responses of dental pulp to operative technics, J. R. Sundell and other Institute scientists find that increased formation of one type of pulp stone appears to be an after effect of tooth repair. Occurring chiefly in the upper part of the tooth, these nodules of calcium are found in healthy and even in unerupted teeth as well as in diseased ones. They begin as a hard, microscopic deposit of calcium salts in one small nucleus of pulp tissue and grow continuously by accumulation of successive layers of calcium. Ordinarily these stones are not harmful unless they become so numerous or large that too little pulp remains to keep the tooth alive and healthy.

A study of 470 human teeth, prepared for an evaluation of the effects on pulp cells of different ways of making a filling, uncovered no correlation between the number of stones and age, sex, or type of operation. However, with the passage of time after all operations, the number of stones increases. Under the microscope it is apparent that a stone, whether large or small, usually occurs within a blood vessel as a plug or as a ring in its wall. This is evidence that damage to the vessel probably triggers the calcification process.

Rickets mechanisms clarified.--It has been known for years that lack of vitamin D results in the soft bones typical of rickets, but recent chemical and X-ray diffraction studies by S. A. Muller and others at Cornell University Medical College explain in greater detail the underlying mechanisms of this bone problem.

Rats raised on diets high in calcium but low in phosphorus and vitamin D have low levels of bone ash and serum calcium, and show other signs of the faulty calcium metabolism of rickets. X-ray diffraction used to compare these rachitic bones with those of normal rats, makes it clear that the size and perfection of bone crystals is improved by vitamin D and impaired by its absence.

Chemical studies also show that more heat produced pyrophosphate is present when vitamin D is lacking. This type of pyrophosphate is considered bo be indicative of the greater chemical

reactivity of immature bone. Normally, rat bones mature in 40 days. During this period, levels of crystallinity increase and those of chemical reactivity decrease. Thereafter, these levels become stable. However, in vitamin D deficient rats, the normal stabilization is approached but not reached even after 60 days.

Study polyphosphate action.--Too much vitamin D is as bad as too little. Among other effects, an excess can cause hard deposits of calcium to form abnormally in such places as the skin or the aorta. Scientists would like to find something that would prevent calcium from accumulating where it is harmful without also interfering with normal bone formation.

Recently, J. T. Irving of the Forsyth Dental Center, Harvard University, with support from the National Institute of Dental Research, and D. Schibler and H. Fleisch of the Schweizerisches Forschunginstitut, Daros, Switzerland, supported by the National Institute for Arthritis and Metabolic Diseases, have reported that polyphosphates such as Graham salt, when given to young rats in doses sufficient to prevent vitamin D-induced calcification in skin and aorta, show no effect on the bone-forming cells. The animals also gain weight normally and appear healthy.

In another experiment, rats with rickets were given either vitamin D, or Graham salt, or both. Cell studies made a week later showed bone healing in the rats given vitamin D with or without the salt, whereas the animals receiving only the salt continued to be rachitic. In this way the scientists showed that Graham salt does not interfere with normal calcification processes or with the cure of rickets by vitamin D, but has promise of becoming a useful experimental drug for treating unwanted calcification in various diseases.

Hereditary defect involves teeth.--A hereditary type of rickets is resistant to treatment with vitamin D. The re-absorption of urinary phosphorus by the kidney is also faulty in this type. People with the defect have soft, deformed bones, low levels of phosphorus in their blood, and also tooth problems.

Institute scientists have made a family study which clarifies the sex-linked mode of inheritance and distinctive dental findings in this disease. Deciduous and permanent teeth that appear normal and are quite free from caries, develop deep, pus-filled pockets at their bases. Internally, their pulp cavities are large, with long horns reaching almost to the dentino-enamel junction under cusps which wear down easily. Much of the dentin is abnormal and globular, and many microorganisms invade the pulp.

H. O. Archard and C. J. Witkop suggest that this hereditary defect should be suspected whenever dental X-rays show large pulps with very long horns, or there are one or more heavily infected

teeth when there is no decay or injury to account for their condition. The diagnosis can be checked by testing the level of serum phosphorus.

Although males usually show the bone and tooth changes, females in the family who are carriers will have low levels of serum phosphorus.

Identify genotype carriers.--Dental Institute studies of unusual defects in teeth help to illustrate some mechanisms of human heredity and improve genetic counselling.

In the slow-developing type of amelogenesis imperfecta, deciduous teeth have a mottled, opaque, milky-whiteness. Not until the permanent teeth appear is the defect fully apparent as a soft, mottled, yellow-brown enamel. This expression of a sex-linked, recessive gene was thought, like baldness, to appear chiefly in males.

Now, careful studies by C. J. Witkop show that a number of females in families with this type of amelogenesis imperfecta have teeth with vertical bands of chalky enamel alternating with regular enamel. These women are believed to be carriers. The alternating vertical bands of normal and abnormal enamel in their teeth represent the activity of one or another of the two X-chromosomes which women have.

The research suggests that other sex-linked dental traits in man and animals should be re-examined for carrier identification.

Periodontal Disease

Periodontal disease is an insidious, destructive, inflammatory process occurring in gums. Eventually it causes teeth to loosen and fall out. The exact cause is unknown, but interactions between various factors including heredity, bacterial reactions, diet, and immunological responses probably account for most cases.

Study structural changes.--Recently K. A. Selvig of the University of Bergen, Norway, made an electron microscopic study of jaws which showed the differences between normal and chronically diseased connective tissues which anchor human teeth. A connective protein called collagen is normally arranged in large, banded, closely packed, thread-like fibrils. In the gum these fibrils are tightly attached to the tooth and extend from it at right angles, becoming looser as the distance from the tooth increases. In periodontal disease, the fibrils, growing smaller and fewer, gradually lose their banded appearance and right-angled positions. Eventually, the smooth edge of the tooth becomes brush-like. The crystals in the tooth mineral also become disorganized in a zone just beneath the ragged surface. Finally, a cuticle is secreted between the connective cells and the tooth which is now exposed to mouth fluids. Little by little, the base of the tooth is more exposed and less attached until it can be moved in its socket and eventually falls out.

Apparently, the agents that break down collagen in the inflammatory process are able to penetrate tooth mineral and to disturb its collagen matrix. However, the loss of crystals is thought due to removal of calcium by local acidic fluids in the tooth pockets where bacterial products accumulate.

Diet factor in calculus.--The formation of dental calculus, or tartar, at the gum line on teeth is often associated with periodontal disease. This hard deposit has to be scraped off or it will gradually force the gums away from the teeth. Some people rapidly form large amounts of calculus and others deposit very little.

Institute scientists studying calculus formation have previously shown that a filamentous bacterium is associated with periodontal disease in certain hamsters fed high carbohydrate diets. Now P. N. Baer and others find that an interaction of factors similar to those operating in dental decay also occurs during most calculus formation in rats. They report that in addition to an inherited susceptibility, and a particular diet, a penicillin-sensitive bacterium appears to be necessary.

Although most rats are relatively free of dental problems, some rats given a high protein diet will form calculus. Without the special diet, calculus rarely occurs. One substrain of Holtzman rat, maintained for some years at NIH, consistently forms more calculus than another Holtzman substrain from Wisconsin, even when both strains are raised on the same calculus-inducing diet and under the same conditions, but are housed in separate cages. However, when the two strains are caged together, the Wisconsin rats form more calculus than usual, though not so much as the NIH rats, which produce the same amount whether in separate or shared cages.

Suspecting that the factor thus transmitted is bacterial, the investigators next fed separately caged NIH and Wisconsin rats high protein diets to which penicillin was added. This treatment reduced the amount of calculus formed by the NIH rats, but had little effect on the Wisconsin rats, suggesting that a penicillin-sensitive, transmissible organism is probably necessary for most calculus in rats. This effect, however, is dependent both on diet and heredity, since animals fed ordinary laboratory chow do not develop calculus, and different strains of rats show quite different susceptibility under the same conditions.

Enzyme isolated from diseased jaws.--Certain enzymes have the role of breaking down tissues. Following the isolation last year of the enzyme, collagenase, from gum tissue, where it destroys collagen fibers in connective tissue, another enzyme, hyaluronidase, has now been found in diseased jaws. A form of hyaluronidase, which is similar to the enzyme operating when a tadpole loses its tail, has long been known to exist in bacteria and lower animals. It breaks down hyaluronic acid, a part of the ground substance in

a number of tissues. Both enzymes are thought to exist in small quantities in normal tissues as part of the repair process but have only recently been isolated from gums. J. Goggins, H. Fullmer, and A. Steffek of the National Institute of Dental Research, who made these findings, are now beginning to study its role in periodontal disease.

Mouth tissues heal rapidly.--Because the mouth is constantly stimulated by mechanical pressures and by bacterial, salivary, and dietary chemicals, it would be surprising if its tissues were not physiologically active. Clinical observations that mouth wounds heal very rapidly may be explained by C. K. Claycomb and others at the University of Oregon Dental School where recent investigations show that rates of collagen synthesis and breakdown are much faster in oral than in most other tissues from the same animal, particularly in young animals.

Scientists find that the ability to make collagen is directly related to the amount of vitamin C present. However, when guinea pigs are deprived of this vitamin long enough to develop scurvy, their gums continue to form some collagen at a reduced rate long after the skin stops synthesis. Also when the vitamin is restored, the rate of synthesis returns to normal much faster in gums than in skin. Even in older animals in which all collagen synthesis and breakdown is slower, collagen activity in the mouth is greater than in the skin. This Institute-supported research helps to explain rapid healing of oral wounds.

Hydrogen sulfide suspected.--A suspect in periodontal disease is bacteria-produced hydrogen sulfide. As an air pollutant, this gas has an offensive odor and can irritate eyes, nose and throat. It is also a by-product of at least five types of microorganisms found in crevices between teeth and gums.

A check of the gingival crevices of a number of people with periodontal disease, who were otherwise healthy, showed that deep pockets (2.0 to 6.0 mm.) contain hydrogen sulfide whereas shallow ones (1.0 to 2.0 mm.) rarely do. Moreover, the lead acetate paper used to test for the presence of the gas turns darkest in the deepest parts of the crevices. A. A. Rizzo of the Dental Institute who reported the presence of the gas in gum pockets is now studying the effects of this bacterial by-product on gum tissues.

Rejection of tooth implants.--An aspect of immunology of concern to dentistry is the rejection of tooth implants. For centuries attempts to replace lost teeth with other teeth have failed. Many have attributed the failure to faulty technique or to selection of the wrong subject because they assumed that teeth have too little organic material to set in motion immunological rejection mechanisms. However, a recent study shows that teeth with all soft tissues

removed do produce immune reactions when they are transplanted into rabbit jaws, and also that parts of teeth, and powdered enamel produce the same effects, as well as the soft tissues within or around teeth. This research clearly shows that in spite of a small organic content, teeth from a different donor do sensitize a recipient, and rejection is to be expected unless the immune response is suppressed or tissues can be in some way matched. These findings of E. White and T. E. Rogers of the Medical College of South Carolina emphasize the need to develop synthetic teeth of non-allergic material as replacements for missing teeth.

Biomaterials Research

Filling-alloy strengths.--A number of studies of dental amalgam by National Institute of Dental Research grant-supported scientists suggest why this time-honored filling material sometimes fails, and point to possible ways to improve it.

Despite the vast temperature changes that occur during eating, the corrosion from saliva, and the extreme pressures of chewing, amalgam fillings are generally satisfactory. However, when they are placed at damaged tooth corners and edges where they are not well supported by tooth structure, the fillings may crack and break under the stresses of biting and grinding actions. This failure is attributed to amalgam's low tensile strength.

Amalgam is not a homogeneous material but consists of separate phases, a silver-tin, a mercury-tin, and a silver-mercury phase. By separately examining the strength of each phase of dental amalgam, National Institute of Dental Research grantees have found that while the silver-tin phase has a greater tensile strength than that of the composite amalgam, the tensile strength of the mercury-tin phase is much lower. It would thus appear that the way to improve the tensile strength of amalgam is by reducing the amount of the weak component.

To study the mercury-tin phase, F. A. Young and L. B. Johnson of the University of Virginia prepared specimens with high purity tin and mercury, tested homogeneity by X-ray diffraction, and determined tensile strength. The highest tensile strength for this phase (10,000 psi) was obtained from a specimen containing ten percent mercury by weight. This figure is only slightly higher than that of composite amalgam. However, at 18 percent mercury content, the amount generally contained in dental fillings, the tensile strength was quite low, only about 4,000 psi.

Etch base for adhesives.--Although at present adhesives will not stick permanently to untreated enamel under the chemical and mechanical stresses found in the mouth, nevertheless some resins bind fairly well to etched enamel. Institute scientists, A. J. Gwinnett and A. Matsui, have made microscopic studies of the

junction between a number of these adhesives and enamel. They report that a thin, outermost layer of enamel is very dense and nonporous. When etched away by a brief treatment with acid, not only is the surface roughened and its area greatly increased, but a looser enamel also is exposed which has minute spaces between the orderly arrangement of crystals.

Some liquid resins are able to penetrate these spaces. Then the liquid hardens and interlocks with the enamel. Several cyanoacrylate and methacrylate resins will penetrate as deep as 25 microns into enamel.

Close-held in this fashion, a resin will protect enamel from mouth chemicals as long as its own stability can withstand mechanical and chemical forces such as chewing and bacterial corrosion.

Model for stress analysis.--Until tooth decay and loss can be prevented, attempts to improve the techniques of tooth repair must continue. The designing of bridges and the shaping of cavities to hold fillings has been learned chiefly through trial and error. Now engineering techniques are being used by R. G. Craig and others at the University of Michigan to explain failures due to stress and therefore to improve the functional design of various restorations. Two-dimensional photoelastic stress analysis is one of these techniques. In this method a model of a particular tooth is made in a special plastic and is exposed to measured amounts of pressure. When a beam of light shines through the resin, changing patterns of dark and light bands form as the pressure changes. This technique enables scientists to measure and compare the directions and concentrations of stresses produced by each level of pressure.

From these studies have come recommendations for improved shaping of teeth in preparation for fillings, inlays, and crowns. These should be more dependable, durable, and comfortable for the patient.

Contributions to Basic Biology

Cell wall lesions.—It is well known that when a suitable mixture of antibody and complement (one of the globulin proteins) occurs in serum, red blood cells lose their contents or lyse. Three years ago collaborating NIH and British scientists who were studying these cells under the electron microscope, found that a series of what appear to be holes, each surrounded by a ring of clear material, develops when this immune hemolysis occurs. The cell contents are thought to pass through the "holes."

Certain gram-negative bacteria are also lysed or killed by antibody and complement in blood serum. When H. A. Bladen and H. Gewurz of the National Institute of Dental Research studied

two of these bacteria, they found the same hole-like lesions surrounded by clear rings. One of these bacteria has an outer membrane consisting largely of a fatty material (lipopolysaccharide) containing a characteristic endotoxin which can cause such immunological reactions as inflammation and fever in mammals. This outer wall can be extracted with phenol and water leaving the bacterial cell intact because it also has a firm inner membrane. Serum can produce the same "holes" in the extracted material as in the surface of the whole organism. There is evidence that antibody triggers this reaction, and that complement enzymes produce the "holes" in the fatty material. The investigators suggest that these complement enzymes also cause such immunological activities of endotoxin as clumping of platelets, aggregating of white blood cells, and changing of the permeability of blood vessels. It is seldom that a structural mechanism can be so clearly demonstrated for a function at the molecular level.

Piezoelectricity.--A concept now being examined by dental scientists stems from the observation in 1941 that wool and hair under stress become polarized and develop electrically positive and negative ends. Inorganic crystals such as quartz also show this pressure type of electromechanical effect, called piezoelectricity--the principle employed in phonograph pick-ups. Piezoelectric effects have also been found in wood, silk, bone and tendon. However, no one knew how mechanical pressure is converted into electricity or the biological significance of the reaction.

This year M. H. Shamos at New York University and L. S. Lavine at the State University of New York, Down State Medical Center, reported that in all these biological materials electricity is generated when pressure is applied at right angles to the axis of long, fibrous, protein molecules aligned in one direction. Apparently, pressure bends the molecules and disturbs their cross linkages, thus displacing their electrical charges. The investigators showed also that when force is applied in the same direction as the axis of these molecules, very little electricity develops, presumably because the molecular cross links are not disturbed very much.

A definite, close-packed, parallel pattern of molecules is easily demonstrated in hard tissues such as collagen in bone and cellulose in wood. But soft tissues also have long molecules which link together much like small crystals. Again the investigators demonstrated that the same piezoelectric effect occurs in these molecules in skin and cartilage.

Discovery of this means of converting pressure into electricity in many types of biological tissues is important because this phenomenon could account for most reactions to mechanical stimuli. For example, piezoelectricity could be the way that sound waves pressing against ear tissues are converted into electrical messages to the brain. Likewise, information from the things we touch and feel may thus be electrically transmitted to the brain. Also, the remodeling of bone under pressure, and the formation of clots following injury to blood vessels are explainable by this process.

Highlights of Research Progress
during 1967

NATIONAL INSTITUTE OF
ARTHRITIS AND METABOLIC DISEASES

## ARTHRITIS

Arthritis and rheumatism, terms that refer respectively to inflammation and destruction of joints and disease affecting tissues adjacent to joints, head the list of chronic diseases in the United States today in terms of social and economic importance. The arthritic disorders, which number almost a hundred, cause widespread crippling and result in a great loss to the economy.

The cause of rheumatoid arthritis, the most chronically painful and crippling of the arthritic diseases, remains an enigma. Recent studies, however, have clarified certain aspects of the disease process, providing important information that may eventually help to explain its etiology.

### Synovial Fluid Research:

Synovial fluid, the lubricating substance present in joints, has been the subject of much fruitful study during recent years. Many chemical components of this fluid have been investigated, resulting in new information about various disorders that affect the joints.

An Institute-supported investigator at Albert Einstein College of Medicine, Dr. J. Sandson, recently detected a heretofore-undefined component of human synovial fluid which is a degradation product of joint cartilage. The component appears to be heavily concentrated only in acutely inflamed joints, such as those seen in gout, septic arthritis, lupus erythematosus, and acute rheumatic fever. This suggests that acute episodes of joint inflammation promote the release of this material from joint cartilage into synovial fluid. It is hoped that by comparing the amount, chemical composition, and turnover of this material in normal and inflammatory synovial fluids, insight might be gained into the effect of inflammation on the metabolism of human joint cartilage.

Arthroscope and Arthritis Diagnosis:

Present methods of studying intra-joint structures for diagnostic purposes have not been completely satisfactory. "Blind" needle biopsy fails to yield adequate tissue for histologic evaluation 5 to 23 percent of the time, while open arthrotomy (incision into a joint) results in postoperative disability, frequent morbidity, and an incisional scar.

This past year, however, Institute grantee Dr. J. J. Clemmons and associates of the University of Vermont have reported 100 percent success in obtaining adequate tissue for histologic examination of intra-joint structures through use of an arthroscope. This instrument, which permits direct visual examination and biopsy of intra-joint structures without recourse to open surgery, has been employed extensively by Japanese physicians in recent years. Adequate tissue for histologic examination and culture was obtained from multiple sites in 24 examinations done on 17 patients with various knee disorders. A totally flexible instrument is now being developed by the grantee scientists which, when perfected, will facilitate visualization and biopsy of the hip joint as well as of additional structures within the knee.

Gouty Arthritis:

Institute scientists led by Dr. J. E. Seegmiller have found that excessive production of uric acid in a number of gouty patients is associated with an enzyme defect. Research in this particular area was stimulated by previous investigations of Lesch-Nyhan syndrome, a tragic inherited metabolic and neurological disease of young males in which a similar enzyme defect and elevated uric acid levels occur.

When the investigators determined the activity of the enzyme, phosphoribosyltransferase (PRTase), in blood cells from gouty patients, they found it to be markedly reduced in a surprisingly large number of patients. Furthermore, some of the gouty patients (those with the least amount of enzyme activity) also showed evidences of a neurological defect that had not previously been recognized as being related in any way to their gout.

Scleroderma:

A chronic disease of connective tissue, scleroderma results in hardening and thickening of the skin and underlying tissue. Internal organs such as the heart, lungs and gastrointestinal tract are also often involved. The skin changes at times lead to muscle atrophy and contraction and limited joint motion which may result in joint deformity.

Although the cause of this disease remains unknown, grantee investigator Dr. Morris Ziff and associates, at the University of Texas Southwestern Medical School, have detected a distinctive abnormality in skeletal muscle capillaries of scleroderma patients which may play a role in the development of this disorder. They obtained biopsies of thigh muscle from eight scleroderma patients; from 48 patients with rheumatoid arthritis, systemic lupus erythematosus, and pulmonary tuberculosis; and from 18 normal individuals. The specimens were then examined with the electron microscope, and a minimum of 18 blood vessels from each specimen were photographed.

The capillary basement membrane showed an abnormal "laminated" appearance in all specimens obtained from the scleroderma patients, and the total number of capillaries was decreased. The investigators believe these variations reflect the loss of typical capillaries, leading to a relative increase in intermediate sized blood vessels. It is still not known what causes these changes, but the findings suggest that scleroderma may develop as the result of underlying blood vessel abnormalities.

## DIABETES

Diabetes research has recently passed through a phase in which significant advances have been made in therapy, most notably the development of oral drugs for better blood sugar control. Currently, the emphasis is upon studies of a more fundamental nature which should lead investigators closer to the underlying cause of the disease.

It is largely in these areas that NIAMD scientists and Institute-supported investigators have made, and are continuing to make, the most significant progress. Adding impetus to ongoing diabetes research projects is the knowledge that there are about four million diabetic patients in this country, as well as an estimated additional five million Americans now living who may later develop the disease in their lifetime.

A complex disorder, for which there is no known cure, diabetes ranks seventh in the list of diseases that cause death. As a result of the body's inability to metabolize carbohydrates normally, the diabetic is inefficient in converting carbohydrates into energy required for normal body functions. The carbohydrates, converted into glucose, accumulate in the blood and spill over into the urine. As the disease progresses, clinically apparent abnormalities in the metabolism of fats and proteins may develop.

In its severe form, untreated diabetes rapidly progresses to a grave metabolic disorder, called keto-acidosis, which may result in coma and death unless controlled by insulin administration and general supportive therapy. In its less severe form, diabetes may also result in accelerated degeneration or "hardening" of the arteries, and, thus, in a greatly decreased life expectancy. Although the disease can be fatal unless properly treated, in most cases it can be well controlled. Today, with proper treatment, most diabetics can lead a normal life and live almost as long as their fellow human beings. Despite good control of clinical symptoms, however, and the usual ability to hold in check the abnormal blood sugar level, the long-term complications of diabetes, primarily affecting blood vessels, peripheral nerves, kidneys, and the eyes, all too often develop relentlessly.

Insulin Secretion:

A number of factors - notably glucose, glucagon, growth hormone, and cortisone - are known to influence insulin secretion by the pancreas. It was first proposed in 1906 that gastrointestinal hormones might have an insulin-releasing effect. Evidence of such an effect, however, was obtained only during the past year. Dr. R. H. Unger, an Institute-supported scientist at the University of Texas, demonstrated that three gastrointestinal hormones secretin, pancreozymin, and gastrin - are biologically capable of triggering insulin secretion in dogs, suggesting that these hormones may play an important role in the priming of insulin secretion following food ingestion. Thus, there may exist in the gastrointestinal tract a chain of hormones capable of stimulating the insulin-releasing cells of the pancreas as required for disposal of high blood glucose or amino acid levels.

The investigator has postulated that this proposed "gastrointestinal-pancreatic axis" may counteract excessive blood glucose or amino acid levels which would otherwise follow ingestion of large meals if pancreatic insulin release were entirely dependent upon elevated blood glucose concentrations.

In a subsequent study the same investigator has obtained evidence of the existence of an as-yet-unidentified intestinal factor, possibly a new hormone, which also acts to augment insulin response to glucose. This material, which functionally resembles glucagon, was isolated from the intestinal tract of dogs and was found to have a greater molecular weight than this pancreatic hormone. The scientist is currently purifying the material and attempting to learn its exact molecular structure.

It would, of course, be premature to attempt to find a role for the newly discovered intestinal factor in the development of diabetes. It is tempting to postulate, however, that an abnormality in the release of this factor could account for the sluggishness of pancreatic insulin response and the glucose intolerance observed in the milder forms of diabetes.

New Diabetes Entity:

A grantee-scientist at Children's Hospital Medical Center, Boston, Dr. Francis X. Fellers, reported a new clinical and biochemical abnormality which is characterized by defective kidney and intestinal glucose transport. Its clinical manifestations include small stature, failure to thrive, reddened cheeks, protruding abdomen, massively enlarged liver, diminished skeletal calcification, extreme flexibility of joints, and massive amounts of glucose in the urine. Although growth is retarded in affected children, mental health is normal. This disorder, termed "pseudo-phlorizin diabetes", because it closely parallels, biochemically, the syndrome induced in laboratory animals treated with phlorizin, appears to be hereditary.

These children apparently produce adequate amounts of insulin and, thus, do not require insulin injections. They appear to benefit from a diet of high protein, vitamin D, sodium fluoride and salt. The major defect appears to be an impairment in glucose conservation by the kidney coupled with defective intestinal absorption of glucose. Studies of this newly discovered type of diabetes are continuing in the hope that they will provide a better understanding of the genetic aspects of diabetes.

Obesity and Diabetes:

There appears to be little doubt that there is a relationship between obesity and diabetes. Most persons who contract the disease after age 40 are overweight, and a significant number of such patients can control their diabetes by weight reduction alone.

It has been known for some time that administration of glucose to persons with mild diabetes results in abnormally elevated blood levels of insulin, an effect that has also been observed in obese nondiabetic individuals. This has led to the theory that insulin action in patients with mild diabetes is somehow inhibited, leading to inefficient transport of glucose into body cells. The nature of this insulin antagonism in such patients has been, and is being, investigated vigorously.

During the past year an Institute-supported scientist at the University of Washington, Seattle, Dr. John D. Bagdade, challenged this theory of an insulin "block" in mild diabetes. He found that elevated blood levels

of insulin in such patients are related only to co-existent obesity and not to carbohydrate intolerance. In these studies, the obese diabetic subjects actually produced less insulin than nondiabetic subjects of identical weight and secreted less insulin in response to glucose administration. This implies that maturity-onset diabetes, like juvenile diabetes, may result from a relative insulin deficiency, rather than from overproduction of insulin possibly combined with a physiologic block of insulin action. This intriguing concept is currently undergoing further exploration.

## CYSTIC FIBROSIS

Cystic fibrosis is an inherited generalized metabolic disorder characterized by an abnormality in the products of all the glands which secrete fluid to external body surfaces, the lungs and the gastrointestinal tract. The abnormalities which are found in these secretions seem to be responsible for the symptoms and signs that plague the patient.

The principal clinical problems seem to relate to the basic metabolic disorder of exocrine secretion. The first of these results from the production of sweat with a high salt content. Due to this defect many patients are unable to conserve salt, especially in hot weather, and are in constant danger of developing profound dehydration, which may lead to death. The unique salty composition of the sweat has, indeed, become the primary source of medical diagnosis of cystic fibrosis with the widespread use of the sweat electrolyte test.

A second, and considerably more serious facet of the disease stems from the abnormal functioning of the mucus-secreting glands of the body. In cystic fibrosis, the mucus-producing glands fail to secrete normal, clear, free-flowing fluid. Instead, they tend to produce an abnormally thick, sticky mucus which obstructs the ducts or openings of the glands. When the thick mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract. This in turn leads to intestinal malabsorption and consequent malnutrition in many patients, with the sequellae of underdevelopment, poor musculature and retarded bone growth.

The third and most important complication involves the lung. Nearly all cystic fibrosis patients develop chronic lung disease at some time during their illness. Thick mucus obstructs the finer air passages in the lung, causing labored breathing and chronic cough. In time, bacteria multiply in the accumulated secretions, and the child falls victim to chronic bronchitis or pneumonia. The latter infection is the leading cause of death in these patients.

New Diagnostic Test:

Early diagnosis and treatment of cystic fibrosis are of utmost importance in order to forestall in part development of irreparable lung damage and other complications. Although the disease is diagnosed principally by the "sweat test" for excessive amounts of salt, such test facilities, are not always readily available and their results are not always conclusive.

Dr. W. J. Warwick at the University of Minnesota, an Institute-supported scientist, recently reported a relatively simple, economical, and efficient sweat test for cystic fibrosis which can be applied routinely to newborn infants. Sweating is induced by applying a heated aluminum cylinder to the infant's back for five minutes. The chloride content of the sweat then is measured directly by applying an electrode to the same area. Results obtained with the procedure are comparable to those obtained with a similar procedure in older children and to those obtained with conventional sweat tests. The test requires only about 10 minutes, is relatively simple to perform, and costs approximately 50 cents per infant. It is hoped that the demonstrated potential of the described procedure will speed development of standardized equipment for such a procedure in the newborn nursery.

Excess Calcium in Salivary Gland:

Institute scientists Dr. Paul A. di Sant'Agnese and associates, in collaboration with scientists from the National Institute of Dental Research, have obtained evidence that excess calcium in the salivary glands of cystic fibrosis patients combines with a certain group of proteins to form an insoluble compound capable of obstructing various organ ducts. Such obstructions might lead to most of the pathological and clinical findings in cystic fibrosis.

A recent study by NIAMD grantee Dr. John A. Mangos and associates at the University of Wisconsin has demonstrated that sweat and saliva from cystic fibrosis children causes rats to excrete saliva with a high sodium content. The implication of this finding is: If there is some factor in the sweat and saliva of children with cystic fibrosis which causes rats to excrete salty saliva, then that same factor may be responsible for the high salt content of the children's own sweat and saliva. This factor, once isolated, may point the way toward elucidation of the inherited molecular defect which causes the disease.

Lead Poisoning Diagnosis:

Dr. H. Shwachman and associates of the Children's Hospital Medical Center, Boston, two years ago reported on a reliable diagnostic aid for cystic fibrosis which involved analyzing samples of toenails, fingernails

and hair for elevated concentrations of sodium and potassium. In an important sidelight, these same grantees have found that latent lead poisoning in young children, often difficult to detect clinically, can be diagnosed by analyzing the hair for its lead content. Chronic lead poisoning, which continues to be an important hazard to the physical and mental health of young children, usually results from prolonged ingestion of lead-containing paint flakes. Although acute lead poisoning is readily recognizable, so called chronic or latent lead poisoning has not been easy to identify. This new method of analysis, which is most useful when results of conventional diagnostic procedures (blood and urine analysis) are equivocal, may thus provide a simple means for screening children with a prolonged exposure to lead containing paint or paint particles.

## OTHER METABOLIC DISEASES

The recognition of hereditary metabolic diseases, as well as the understanding of the mechanisms, by which they produce symptomatology, has increased immensely over the past half century. Further emphasis needs to be placed on early recognition of these "inborn errors of metabolism" inasmuch as improved medical management can delay the onset of complications and even permit a longer survival in some instances. Institute and Institute-supported scientists have been particularly productive this past year in their studies of this group of diseases.

Institute scientist Dr. Leonard Laster and associates have identified a previously unrecognized fatal disease of children and discovered its underlying biochemical cause. Called sulfite oxidase deficiency, the disease is characterized by severe mental retardation, dislocated eye lenses, and early death. The biochemical abnormality is a deficiency of sulfite oxidase, the enzyme which normally catalyzes conversion of sulfite to sulfate. Sulfite oxidase deficiency joins two other causes of mental retardation, homocystinuria and cystathioninuria, as diseases of the metabolism of sulfur-containing compounds.

Another team of Institute scientists headed by Dr. J. R. Seegmiller has linked the neurological symptoms of a fatal disorder of the nervous system, Lesch-Nyhan disease, to a biochemical defect in brain tissue. The primary defect associated with the major neurological symptoms, the scientists found, is a complete absence of the enzyme hypoxanthine-guanine phosphoribosyltransferase (PRTase) in basal ganglia of the brain. PRTase normally plays an important role in the metabolism of purines, building blocks of the body's hereditary mechanism. Development of effective therapy for this tragic familial syndrome of young males will depend on further delineation of the relationship between PRTase deficiency in the basal ganglia and the clinically apparent neurological disease.

Dr. Seegmiller and his associates have also uncovered an enzyme deficiency in children afflicted with maple syrup urine disease. This disease, a rare familial metabolic disorder, is characterized by progressive cerebral dysfunction and excretion of urine with an odor like that of maple syrup. Biochemically, these children show elevated blood and urine levels of certain amino acids and of their corresponding keto acids. The presence of these metabolites has suggested a defect in the enzyme responsible for the further metabolism of these keto acids to carbon dioxide. Such a defect has now been demonstrated in leukocytes and in fibroblasts grown from skin explants obtained from a child with this disorder. The current work suggests that absence of this enzyme in afflicted individuals may be one of the basic factors underlying the pathogenesis of maple syrup urine disease.

Idiopathic hemochromatosis, or "bronze diabetes", is an uncommon, chronic and progressive disorder characterized by excess deposition of iron in most tissues of the body, increased pigmentation, cirrhosis of the liver, pancreatitis, and, diabetes mellitus. Dr. A. Mazur and other Cornell University scientists supported by the Institute have described a specific metabolic defect in this disorder. Their investigation demonstrated that afflicted patients are deficient in hepatic xanthine oxidase, an enzyme which releases iron stored in the liver. The investigators propose that hemochromatosis may be the result of a genetic defect characterized by failure to develop normal amounts of hepatic xanthine oxidase.

Therapy in Wilson's Disease:

D-penicillamine, a chelating agent which promotes urinary copper excretion, is generally accepted as effective therapy for Wilson's disease, an inherited disorder of copper metabolism causing progressive neurologic and liver disease. Studies by Institute-supported scientist Dr. I. H. Scheinberg and associates at the Albert Einstein School of Medicine have demonstrated that prolonged daily administration of this agent can delay or even prevent development of clinical manifestations of Wilson's disease in genetically and biochemically predisposed relatives of patients with this disorder.

In their investigation, the scientists treated 42 of 53 asymptomatic subjects, who had the chemical abnormalities associated with the disease or a positive family history, with a low copper diet and one gram of D-penicillamine orally per day. All of the subjects were followed from 3 to 10 years, after which overt manifestations of Wilson's disease were found in the 11 untreated subjects (all of whom were under the care of other physicians), with death due to the disease occurring in five cases. No significant manifestations occurred in any of the 42 treated subjects. Moreover, studies based upon the natural history of 121 known Wilson's disease patients indicated that at least 8 of the treated subjects would have been expected to develop symptoms had they gone without therapy.

GASTROENTEROLOGY:

Gastroenterology - the study of the gastrointestinal tract, and associated glands and organs, including the liver, - is as complex from the standpoint of the biomedical research investigator as it is from the point of view of the practicing physician. The diversity and magnitude of gastrointestinal disorders combine to place these diseases at a prominent point among the chronic and disabling afflictions occurring in man.

Liver Disease and Transplantation:

Previous research has demonstrated the technical feasibility of liver transplants. Survival time in these studies has been severely limited by a multiplicity of factors, the most important of which has been the failure to obtain good immediate liver function postoperatively. The past year, however, has seen the first enduring liver transplants.

Dr. Thomas Starzl, an NIAMD-supported scientist, and associates at the University of Colorado Medical Center, reported successful liver transplantations in four children with a survival time of many months. The investigators credited a combination of improved methods of immunosuppression, organ storage, tissue typing, and operating technique for the newfound success.

Although the long-term prognosis is unknown as yet, the fact that these liver transplants have continued to function long beyond that achieved in earlier transplants holds significant promise for the future.

Treatment of Hepatic Coma:

A major problem faced by physicians is the maintenance of victims in hepatic coma due to acute liver failure until their own livers can be restored to normal function. Dr. J. C. Darin and associates at Marquette University reported success in the past year in therapy of patients in hepatic coma through use of an extracorporeal hepatic support system utilizing a cadaver liver. Dramatic results were achieved, the Institute-supported investigators reported, in three of four cases. The procedure involved cannulating the patient's femoral artery and saphenous vein. The blood, flowing from the femoral artery through tubes to a heat exchanger to elevate its temperature slightly, enters the cadaver liver through the hepatic artery and portal vein and, after exiting through the hepatic veins, is pumped back into the patient's saphenous (leg) vein.

In three instances the comatose patients became conscious and their own livers began to show inproved function. Despite this, all patients subsequently died of causes not directly related to hepatic failure. The success of this perfusion procedure could prove particularly beneficial

to hepatitis victims, who may develop hepatic failure and coma following only a single injury and whose livers may heal to resume normal function when inflammation, infection, and increased metabolic demands have subsided. The technique also may aid patients suffering from chemical injury to their livers, such as occurs in carbon tetrachloride poisoning, patients in liver failure following portacaval shunt, and, possibly, candidates for liver transplants by improving their pre-operative condition.

Diagnosis of Gastrointestinal Hemorrhage:

A major challenge confronting physicians is the early diagnosis of the site of gastrointestinal bleeding. Recent studies have indicated that the source of such bleeding escapes detection in 15 to 40 percent of patients studied. Institute-supported investigators Dr. M. Nusbaum and associates at the University of Pennsylvania have now found abdominal angiography to be a safe and valuable diagnostic procedure for pinpointing the site of gastrointestinal hemorrhage in patients who are actively bleeding at a slow rate.

The technique involves use of a radio-opaque catheter (with premolded tip) that permits selective catheterization of almost any branch of the aorta. The catheter is introduced into the femoral artery and then, under fluoroscopic control, into the celiac axis and later into the superior mesenteric artery (two branches of the aorta which supply the GI tract). Injections of radio-opaque dye are made into each of these arterial trees and serial film exposures are made every second for 18 seconds, are processed immediately, and are compared.

Using this technique, the investigators were able to find the source of gastrointestinal bleeding in 18 of 21 patients studied, identifying such sources of blood loss as a mucosal tear near the gastro-esophageal junction, benign stomach ulcers, "stress ulcers" in a postsurgical patient, rupture of the spleen, and rupture of a splenic artery aneurysm.

The procedure also was found to be of particular value in studying patients with cirrhosis of the liver, and in detecting or excluding the presence of bleeding esophageal varices (dilated veins at the gastro-esophageal junction). Additionally, the investigators found that the procedure, which takes only 30 to 40 minutes, does not interfere with other methods of examination or required surgery. In fact, the investigators suggest, the procedure may aid the surgeon greatly by localizing the actively bleeding area and, thus, may prevent time-wasting exploratory surgery.

Surgery for Dumping Syndrome:

A severe and disabling aftermath of ulcer surgery is a condition known as the "dumping syndrome", which develops in up to 70 or 80 percent of those patients requiring partial stomach resection for peptic ulcer. This surgically-induced disturbance of pyloric function results from an inability to control the rate of gastric emptying and leads to a painful sense of abdominal fullness, nausea, belching, profound weakness and trembling, profuse sweating, palpitations and, at times, sudden and massive diarrhea.

Dr. Edward A. Stemmer, an Institute-supported scientist and associates at the University of California College of Medicine at Los Angeles, in the past year devised an effective remedial surgical procedure for this syndrome which should be considered for the patient in whom conventional diet and drug therapy has failed. In their study, the investigators observed four patients with symptoms so severe following vagotomy and pyloroplasty that they could not continue in their usual occupations. Selecting two of the patients, the investigators interposed a 4 centimeter segment of jejunum between the stomach and duodenum in a reversed "tail-to-head" position (which thus had peristaltic movements in a retrograde, reversed direction), in order to simulate the normal function of the intact pylorus (stomach-outlet). Although gastric retention was a problem in the immediate post-operative period, the dumping syndrome disappeared within a few days in both and has not recurred in 16 and 24 months, respectively.

Ulcerative Colitis:

One of the commonest chronically debilitating disorders of the gastrointestinal tract is ulcerative colitis, a progressive inflammatory disease of the colon or large bowel. Of unknown etiology, the disease is characterized by severe cramps, repeated bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals. Although the disease continues to resist efforts to discover its cause, progress is being gradually achieved in therapy which is aimed primarily at correcting mineral and nutrient loss, controlling diarrhea, preventing infection, and ministering to the patients' psychologic needs.

During the past year, research by Institute grantee Dr. H. J. Binder and associates at the Yale University School of Medicine, New Haven, Conn. suggested a possible link between milk intolerance and the symptoms of ulcerative colitis. Milk intolerance, a relatively common syndrome in certain otherwise normal adults and in patients with inflammatory bowel disease, is known to result from a deficiency of the intestinal enzyme lactase which converts lactose, or "milk sugar", into glucose and galactose. In the investigation, 39 patients with ulcerative colitis or proctitis were

studied to determine whether in any way lactose intolerance might be a factor which contributed to their diarrhea. Their findings showed that 59 percent of these patients had lactose intolerance. Follow-up evaluation 6 to 16 months after institution of a lactose-free diet, which resulted in a major improvement in the patients' symptomatology, indicated that the only patient who did not have a major remission during the study had failed to follow the prescribed lactose free diet. The results show that the inflamed, irritated bowel in ulcerative colitis often cannot handle the osmotic load, and that lactose intolerance imposes an extra burden upon the inflamed bowel. On the basis of their study, the investigators advise a lactose-free diet in ulcerative colitis patients who also have lactose intolerance.

Although this study does not necessarily implicate intestinal lactase deficiency as a causative factor in ulcerative colitis (this deficiency may be secondary to the underlying prime disorder, and, in fact, intestinal lactase deficiency is known to develop as an aftermath of a number of other primary debilitating diseases), this finding opens up a new, promising approach to better symptomatic treatment of patients with ulcerative colitis.

## KIDNEY DISEASE

During the last five years, diseases of the kidney, and especially end-stage kidney disease, have come to the forefront of attention for both Federal and non-Federal research and service efforts. Much of the impetus for this increasing interest in kidney diseases has come from the development of two dramatic but expensive therapeutic approaches to end-stage disease, chronic hemodialysis and kidney transplantation. The partial successes of both techniques, coupled with other research advances leading to a better understanding of kidney disease, have led to a proliferation of activities directed toward reducing the morbidity and mortality these cause in the population.

### Severe Renal Complications Averted:

The development of peripheral neuropathy is a serious complication of chronic renal insufficiency, and previously, chronic hemodialysis had been incriminated as a cause. Institute grantee Dr. R. H. Jebsen and his associates at the University of Washington, Seattle, however, have now obtained evidence to indicate that intensive long-term intermittent dialysis may arrest or prevent development of peripheral neuropathy. The scientists recommend that dialysis be instituted early in uremic patients who develop this complication, and that it be intensified in those in whom neuropathy progresses. With earlier and more intensive dialysis therapy, it is believed that such neuropathy might be rendered a rare and mild complication of chronic renal failure.

Folic Acid Needed in Diet:

Another Institute grantee, Dr. C. L. Hampers of the Harvard Medical School, Boston, has shown that anemic patients in chronic renal failure are deficient in folic acid, that this deficiency may be aggravated by chronic, long-term hemodialysis, and that red blood cell and platelet precursors respond to folic acid supplementation. Chronic renal failure is often complicated by a type of anemia believed to result from failure of the bone marrow to form blood cells normally. Examinations of many such marrows have shown a tendency for developing blood cells to be large and disproportionately immature, suggesting that vitamin $B_{12}$ or folic acid deficiency may be a factor in their maldevelopment. The present study has established that patients in chronic renal failure, particularly those with anemia who are undergoing periodic hemodialysis, have low serum levels of folic acid and that this vitamin is dialyzable in a hemodialysis system. Since considerable folic acid is lost in this manner, this vitamin probably should be added to the diet of such patients.

Kidney Stones:

Kidney stones remain an important urologic problem since they usually cause severe pain and may often lead to recurrent kidney infection and ultimate kidney destruction.

Institute grantee Dr. S. N. Gershoff at Harvard University, Boston, has reported a reduction in the rate of stone formation in patients susceptible to stone formation through daily oral administration of magnesium and vitamin $B_6$ for prolonged periods of time. In earlier studies the Institute-supported investigator had shown that experimental induction of renal stones in rats could be prevented completely or partially by large amounts of the above substances in the diet. They now report that 30 of 36 patients on this regimen for at least five years have shown no recurrence, or decreased recurrence, of kidney stones. All patients had previously formed two or more stones per year for at least two years.

Transplantation Advances:

With presently available methods of immunosuppressive therapy it is often possible to prevent or reverse the initial, acute rejection of a kidney transplanted from one genetically nonidentical individual to another. This therapy, now relatively well standardized in most centers engaged in clinical transplantation, permits the survival for more than twelve months of 65 percent of renal allografts donated by a member of the recipient's immediate family and slightly less then half the kidneys donated by unrelated persons or derived from cadavers. This partial success in controlling early transplant rejection has now brought to light evidence of more subtle and chronic forms of immunologic attack upon the transplant that occur despite long-term immunosuppressive treatment.

Institute grantees have found that chronic transplant rejection (in contrast to the well-known acute rejection crises), evidenced by proteinuria and nephrosis, occurs frequently in kidney transplant patients who have survived for more than three months or even years. The amount of proteinuria seems to be related to the degree of incompatibility between graft and recipient rather than to original kidney disease. The present study has alerted investigators against complacency in cases of apparent success in kidney transplants where the postoperative course was not characterized by conspicuous, acute rejection crises.

THE ARTIFICIAL KIDNEY:

This year marks the second anniversary of the inauguration of the Institute's Artificial Kidney Program, when a centrally managed and planned effort was launched to develop a simpler, more effective and economical artificial kidney than was then available. Significant contributions toward that goal have been accomplished.

"Capillary" Dialyzer:

This past year a team of scientists working with support from an Institute Artificial Kidney Program contract reported initial success in clinical trials with a new capillary artificial kidney. This newest dialyzer is a compact cylinder packed with 11,000 hollow cellulose fibers. The patient's blood is routed through these fibers where it is cleansed by a dialyzing fluid bath and the waste products are extracted.

The procedure is similar to that employed by conventional artificial kidneys, which, however, are considerably larger and some of which require considerable set-up and sterilization time. This small, compact and potentially disposable unit appears just as effective in preliminary clinical trials as conventional artificial kidneys. In addition, it offers marked potential advantages through its low blood priming volume (which obviate blood wastage and a high rate of compensatory blood transfusions), ease of operation, and disposable nature. The investigators believe that their capillary kidney can be operated by the patient's own heart without need for an additional blood pump.

High Efficiency Dialyzer:

Another group of Institute contractors, Drs. A. L. Babb and L. Grimsrud of the University of Washington, Seattle, have developed a compact, high-efficiency dialyzer that permits treatment of almost twice as many patients in a given dialysis center setting as with conventionally used dialyzers. This dialyzer is considerably smaller than previous models and decreases the time required for cleansing the blood of impurities.

The Babb-Grimsrud (B-G) dialyzer named for its developers measures only 20 by 50 centimeters. It is constructed of plastic and a commercially available foam nickel support material. Requiring a total blood volume of only 70 cc, it decreases the presently high blood priming requirement and the need for compensatory blood transfusions. It costs half as much as the conventionally used two-layer Kiil dialyzer, can be assembled in ten minutes and can be sterilized in an autoclave.

Compared to the Kiil dialyzer, the B-G dialyzer has approximately one-third the membrane area, one-seventh the blood volume, and one-fourth the weight, with no decrease in urea clearance and only slight decreases in creatinine clearance. At the present time a series of the new dialyzers are being produced for extensive testing under routine operating conditions.

New Re-use Procedure:

Earlier this year, a group of Institute grant-supported scientists headed by Dr. B. Scribner at the University of Washington, Seattle, reported a new technique for storing and re-using conventional artificial kidney equipment which reduces the cost and simplifies the work involved in performing hemodialysis, particularly in the patient's home. The new procedure permits re-use of the artificial kidneys for at least three successive dialyses, requires assembling and disassembling of the unit only once instead of three times a week, and allows use of blood tubing sets at least nine times, for an estimated saving of $800 per patient per year.

Ordinarily, conventional artificial kidneys are disassembled completely after each use, and the old membranes and blood tubing are discarded. Before the next treatment, the machine must be re-assembled, resterilized, and equipped with new membranes and blood tubing.

The new technique has proved successful in more than 150 dialyses on ten patients, with individual dialyzers having been used as many as six consecutive times. Time and effort in preparing for dialysis have been reduced by 30 percent and future automation of the technique should further reduce such work by another 30 percent. This double saving is particularly significant in home dialysis where, in the past, the preparation of a fresh artificial kidney for a dialysis treatment required several hours of time and effort.

ENDOCRINOLOGY:

Endocrinology concerns itself with the study of the endocrine glands, their secretions - the hormones - and of the effect of these secretions on the metabolism and physiology of man.

Mode of Action of Thyrocalcitonin:

This past year, significant advances have been made in the delineation of the physiologic role of a newly discovered hormone, thyrocalcitonin. This hormone was discovered in 1963, by Institute grantees who subsequently showed it to be a product of the human thyroid gland which acted to lower blood levels of calcium.

Institute scientists Dr. G. D. Aurbach and Dr. J. O'Riordan have now shown that thyrocalcitonin does not actively remove calcium from the blood, but appears to impede the normal process of transfer of bone calcium from the skeleton to the blood. (This resorption of calcium from bone is one normal source of blood calcium; the other is calcium contributed directly by the diet). If thyrocalcitonin can be shown to have a potent inhibiting effect on the release of calcium from bone, it might prove in the future to be of therapeutic value in the treatment of disorders marked by excessive breakdown of bone of a limited time period, such as the bone demineralization associated with prolonged bed confinement after major injury.

Lactase Deficiency and Osteoporosis:

Other Institute scientists, Dr. G. D. Whedon and associates, have obtained evidence to indicate that intestinal lactase deficiency, resulting in milk intolerance, may provide one basis for the development of osteoporosis, a disorder characterized by a gradual decrease in both the amount and strength of bone tissue affecting middle aged and elderly persons. Several investigators have proposed that a long-term dietary deficiency of calcium might be one cause of osteoporosis, but hormonal and other nutritional factors also play a role. Evidence has now been gathered to indicate that in some patients, namely those with a deficiency of the intestinal enzyme lactase, osteoporosis may principally result from prolonged abstention from milk ingestion, instituted voluntarily in order to avoid the symptoms of milk intolerance. In such individuals, this abstention would result in chronic calcium deficiency and subsequent osteoporosis.

Gonadotropins:

Gonadotropins are hormones that stimulate the sex glands. Production of gonadotropins, normally a function of the pituitary gland, may also be found in association with tumors in any one of the endocrine glands.

Institute scientist Dr. Saul W. Rosen has recently described the first documented instance of gonadotropic activity of a non-endocrine tumor, specifically a carcinoma of the lung.

Four male smokers with gynecomastia (breast enlargement) and lung cancer, as well as ten patients with lung cancer and no gynecomastia were studied. Blood, urine, and pituitary and lung tissue were examined for gonadotropic activity in all patients.

The study showed that all patients with gynecomastia had elevated levels of gonadotropins in the urine and three of the four patients had elevated levels in their lung tumors. All ten patients with lung tumors unaccompained by gynecomastia were found to have normal levels of gonadotropins. This study has served to alert physicians to search for lung tumors in any elderly male smokers with gynecomastia.

Highlights of Research Progress
during 1967
on
Neurological and Sensory Disorders

Disorders of Vision

NINDB support for vision research scored heavily twice in 1967 when a current grantee and a former grantee won two of the internationally coveted awards for scientific achievement, the Nobel prizes for medicine. Haldan Keffer Hartline, an NINDB grantee at the Rockefeller Institute for Medical Research, New York City, was honored for his success in demonstrating the reaction pattern of individual visual cells in relation to quantity and quality of light. George Wald of Harvard University, the former grantee, received his award for his contribution to the understanding of light's activation of photo-receptive cells in the retina and for his development of knowledge of color blindness.

Not as dramatic in outcome but highly important in terms of achievement were other significant accomplishments in vision research by NINDB-supported scientists during the year.

Through animal studies at the State University of New York, Buffalo, Dr. Werner K. Noell proved that light above a certain intensity irreversibly damages the retina. In terms of the possible influence of intense light on the visual cells of man, the implications of this discovery are far-reaching.

The chances for the successful repair of large retinal detachments were greatly increased through the achievements of two teams of Boston scientists headed by Drs. C. L. Schepens of the Retina Foundation and H. MacKenzie Freeman of the Massachusetts Eye and Ear Infirmary. They advanced the techniques of preoperative examination, preoperative management, surgery, and postoperative care in cases of giant retinal breaks so successfully that cases previously thought inoperable may now be considered, bringing new hope to many.

The diagnosis and treatment of glaucoma advanced considerably during the year, bringing scientists closer to an understanding of the mechanism of this disease than ever before. Particularly valuable in staying the advances of glaucoma were the research studies evaluating the effectiveness of new and older drugs used in maintaining proper intraocular pressure by such scientists as Dr. Bernard Becker at the Washington University School of Medicine in St. Louis. Dr. Becker and a team of specialists found a new drug, isosorbide, to be a useful agent in acute primary and secondary glaucoma, and as a preoperative

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medication for various types of eye surgery. The agent has a number of advantages over other agents: it can be administered orally in a doctor's office, and in cases of acute glaucoma it brings down the intraocular pressure rapidly. Too, it can be used without complications with diabetics.

The need for further investigation of the efficiency of the three tonometric procedures most frequently used to find suspected cases of glaucoma among the population was affirmed through such community-wide studies as those conducted under the leadership of Dr. J. Theodore Schwartz from NINDB's Epidemiology Branch. To enhance knowledge in this important area, cooperative efforts to standardize those examination procedures which are useful as screening devices will now be undertaken.

Pediatric ophthalmology gained through advances in scientific methods for evaluating vision loss in infants. The clinical usefulness of two important new electrophysiologic methods--electroretinography (ERG) and the evoked-occipitogram (EVOG), was demonstrated through a 2-year study of infants and toddlers, conducted by Drs. J. Lawton Smith, Department of Ophthalmology, University of Miami School of Medicine, and Thorne Shipley, Ophthalmology Section, Yale University School of Medicine.

The case for early diagnosis, treatment, and surgery for eye disorders of children received strong support through studies by Drs. Torsten N. Weisel and David H. Hubel of the Harvard Medical School, who proved that pattern perception is the function of the cortical cells and occluded or unused (amblyopic) eyes quickly lose connection with these cells. Robert N. Shaffer's demonstrations at the University of California, San Francisco, of the need for early correction for congenital glaucoma to prevent nonuse of the weaker eye also supported this changing approach to the medical management of infant eye disorders.

When intraocular pressure in juvenile diabetics--an almost completely overlooked area of ophthalmological investigation--was studied at the Albert Einstein College of Medicine by a team headed by Dr. Aran Safir, the investigators uncovered significantly elevated tension in one-half of the 70 juvenile diabetics tested. The study demonstrates the importance of ophthalmological attention to children suffering from this disease.

A simple test to determine when high oxygen therapy reaches a danger point to the eyes was developed by Dr. Arnall Patz and his associates at the Wilmer Eye Institute, Johns Hopkins University and Hospital, Baltimore. Such therapy is often necessary in order to save the lives of premature infants afflicted by a respiratory distress syndrome known as hyaline membrane disease--a disorder which strikes

some 40,000 premature babies annually in this country. (It was this disease which caused the death of John F. Kennedy's son, Patrick.) By looking through a simple hand instrument, the ophthalmoscope, into the back of the eye, physicians can now determine when excessive oxygen is being delivered. Dr. Patz found that the retinal blood vessels show severe constriction when excess oxygen levels occur. Previously, the only method of determing oxygen toxicity was to measure the arterial blood oxygen content. Only a few hospitals are equipped to do this for the technique requires a highly skilled pediatric team, special training in analyzing the blood content, and expensive instruments.

Investigations of the human macula at the University of California San Francisco Medical Center added to our understanding of the degenerative changes which take place in the eye as a consequence of aging. Electron microscopic studies of Bruch's membrane, a transparent inner layer of the choroid, showed that two types of collagen (the main supporting protein of the skin) accumulate with increasing age. With this accumulation the elastic layer of the membrane becomes less distinct.

Regenerative processes were also the subject of some NINDB-supported studies. Scientists at Harvard Medical School and the Department of Neurosurgery, Massachusetts General Hospital, Boston, reevaluated the ocular status of survivors of acute third nerve palsies due to intracranial aneurysms and found that regeneration eventually occurred in practically all patients. They also found that there are certain methods of initial treatment which will enhance recovery.

Since uveal ganglion cells are rarely found in sections of normal eyes, the recent discovery of diffuse overabundance of such cells in five cases of malignant melanoma (tumors) of the choroid in relatively young persons indicates the possibility of congenital predisposition of some eyes to such malignancies. The discovery represents another advance in the search for the origin as well as the early clinical detection of malignant ocular melanoma.

At least one important possible link in the chain of events leading to diabetic retinopathy, along with a new concept of the role of microaneurysms, appears to have emerged through a study headed by Dr. Thomas Behrendt, Jefferson Medical College. This study of fluorescein in retinal circulation utilizes a highly refined sequential photography technique and spectral reflectance photography. A most striking feature of the new method is the large number of patent vessels that can be seen filling with dye. These two techniques point strongly to the existence of large areas of edema invisible by conventional ophthalmology and fundus photography. Analysis of filmed records produced by this new method are serving to pinpoint the behavior of microaneurysms in the development of diabetic retinopathy.

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When treatment given cases with dislocated lenses at the Johns Hopkins Hospital in Baltimore over a 12-year-period was evaluated, an alarming disparity in methods used and results obtained was found. This led the principal investigator, Dr. William H. Jarrett of the Wilmer Eye Institute, to propose an entirely new set of guidelines for the management of future cases, covering a diverse number of situations with a variety of suggestions for treatment.

A new method of freezing corneal tissues at a precisely controlled rate of minus 190 degrees has kept corneas donated for transplants "alive" in suspended animation over considerable periods of time, according to Dr. Herbert Kaufman, University of Florida, Gainesville. Corneal tissue preserved in this fashion has been found as suitable as fresh tissue and has greatly extended this method of treatment.

In an effort to better define those ocular abnormalities which may indicate the presence of systemic lupus erythematosus, a degenerative process of unknown etiology, which involves the smaller blood vessels and connective tissue, Dr. George L. Spaeth, Ophthalmology Branch, NINDB, found that corneal lesions form an important part of the clinical picture. More than half of the persons with the disorder who were hospitalized at the National Institutes of Health were found to have symptoms of corneal disease, while almost 90 percent had pathological staining of the cornea with fluorescein. Other ocular signs and symptoms were also found.

The worth of routine use of antibiotic drugs at the time of intraocular surgery as a means of reducing the incidence of post-operative infection was clearly demonstrated by a team of scientists at the Washington University School of Medicine who evaluated over 3,000 cases of eye surgery performed at the McMillan Hospital, St. Louis, over a period of 4 years.

Phagicin, a totally new type of antiviral agent which looks promising for the improvement of treatment of corneal ulcers, has been tested successfully by doctors at the University of Florida.

Usefulness of ultrasound techniques in confirming or discovering abnormalities in eyes in which visualization of the posterior segment is impossible was demonstrated in a recent study at the Wills Eye Hospital in Philadelphia. When scientists there sought to correlate ultrasonic findings with subsequently demonstrated histopathology of enucleated eyes having opaque media, they found that the ultrasonographic diagnosis correlated with the findings of microscopic tissue studies in 77 percent of cases. They concluded that while all pathologic states cannot be differentiated by ultrasound at present, with refinements in the technique and additional experience in its use, ultrasound should become an increasingly valuable tool in diagnosing eye disorders, particularly under those conditions where other diagnostic techniques cannot be used.

Recent clinical observations and primate experiments by NINDB-supported scientists indicate that multiple motor systems probably exist in the extraocular muscle of man and primates. This concept may provide new diagnostic formulations and the logic for further research into the physiology of the oculomotor system.

Collaborative Perinatal Project

A giant study of mothers and their babies has uncovered a number of new clues in the search for the causes of birth defects this past year. More has been learned about the causes of prematurity, how to identify high-risk mothers, and the effect on the offspring of certain maternal disorders during pregnancy.

Especially significant to scientists in the Collaborative Perinatal Research Project is added knowledge on the role of prematurity and low birth weight in the production of neurological defects. In the Project, a joint endeavor of 14 medical centers and the NINDB, 30 percent of one-year-old babies with neurological problems were born prematurely. More than two dozen variables were checked in the Collaborative Project and found to have some correlation with birth weight. For example, smoking was found to have a pronounced effect on birth weight, confirming several other studies on this point. Women who smoke cigarettes during pregnancy give birth to more babies classified as premature than do non-smoking women. This may be a result of nicotine which is known to pass through the placenta into the body of the growing baby before birth, or because the high level of carbon monoxide in the mother's blood reduces the amount of oxygen carried to the unborn child, or to other causes.

Project scientists also are more convinced of an association between birth weight and IQ. In children with full-term gestations, the IQ was found to vary with birth weight. In identical twin sets, the member with the lower birth weight and smaller head was found to have the lower IQ. This supports earlier studies on the relationship between birth weight and intelligence which is independent of gestational age. The effect cannot be attributed to prematurity. In twins, the sharing of nutrients is unequal, but both will suffer since two rather than one drain maternal supplies. However, one will suffer more than the other.

Another important finding is that a number of maternal disorders--particularly diabetes and gall bladder disease--may alter the nutrient supply to fetus to cause mental retardation in certain cases. Intellectual and neurological function was affected in children of diabetic mothers who had episodes of acetonuria (an excess of acetone bodies in the urine). No such effect was observed in those whose mothers were free of acetonuria.

In a study of 40 maternal deaths in the Project, it was found that 28 had been identified as high-risk mothers before conception. The deaths of these known high-risk mothers might have been prevented through medically advised family planning and adequate preconceptual care. Project scientists conclude that many such deaths could be prevented through more and better family planning services. This study was reported by Drs. R. F. Vollman and J. G. Marmol, investigators in the Collaborative Project.

Inborn Errors of Metabolism

Rapid blood tests to diagnose two genetic disorders causing mental retardation and other symptoms have been developed this year by an NINDB scientist at the Institute's Bethesda laboratories. Dr. Roscoe O. Brady has developed these tests to identify patients with Gaucher's and Niemann-Pick's diseases, and has identified the metabolic defect causing a third disorder--Fabry's disease.

Other developments this year include initiation of an information service by the Institute-supported Brain Information Service at the University of California. A system for classifying the biochemical abnormalities present in inherited neuromuscular disorders has been developed by another group of investigators.

These recent findings are resulting from studies at NINDB and at medical institutions throughout the world to identify the exact chemical errors producing a variety of hereditary metabolic disorders and to develop effective methods of diagnosing and treating them.

Dr. Brady and scientists at the Weizmann Institute of Science, Israel, developed the blood tests which accurately determine whether a patient has Gaucher's or Niemann-Pick's disease. Presently, these tests are being conducted with blood preparations from patients all over the world suspected of having these disorders. Further studies are under way to determine whether the same tests can be used to detect carriers of the familial disorders.

The same team of investigators, under the direction of Dr. Brady, have not only identified the metabolic defect in patients with Fabry's disease but have also developed a test which diagnoses the disorder and detects carriers. The researchers found in Fabry's patients an extreme deficiency of an enzyme required for the disposal of aged red blood cell membranes. Since the disease is linked to the X (sex) chromosome, it is transmitted from mothers to their male offspring. Tests of these mothers show they also have decreased enzyme activity (25 percent of normal) which permits physicians to tell that they are carriers. The same test accurately diagnoses patients with the disorder.

The finding last year by Dr. Brady of a deficiency of sphingomyelinase activity in tissues of patients with Niemann-Pick's disease has now been confirmed by investigators at Harvard University. Investigators suggest that specific organ transplants may be one way of remedying the enzyme deficiency in patients with any of these inborn errors of metabolism. Other suggested future treatment methods include possible test-tube synthesis of the deficient enzyme and regular administration to the patient, as insulin is given to diabetics, or the administration of an appropriate DNA or RNA to correct the hereditary error.

Custom-tailored bibliographies and other data concerning studies of the major biochemical pathways of the central nervous system and major regions of the brain will be available to scientists through the new information service established by the University of California's Brain Information Service. Data on investigations of specific enzymes, enzyme systems, and brain regions will facilitate scientist-to-scientist communication in these fields.

A newly developed classification system for the biochemical abnormalities present in inherited neuromuscular disorders is designed to show whether the defect is present in one or many neuromuscular diseases, and to define the importance of the biochemical error in treating the disorder. The system, developed by Drs. W. King Engel and Martin A. Hatcher of the Institute's Medical Neurology Branch, should permit easy integration into a central registry of newly discovered biochemical abnormalities associated with inherited muscle disease. Drs. Engel and Hatcher have suggested that published classification of these abnormalities be updated annually and distributed to interested biomedical scientists.

Head Injury

Whiplash, as well as concussion, can cause severe damage in head injury victims, Institute studies show. In fact, whiplash injury may produce concussion and cerebral hemorrhages. Direct impact injury without concussion is less likely to produce hemorrhage than whiplash injury. Experimental studies conducted under the direction of the Institute's Branch of Surgical Neurology at its Bethesda laboratories have shown that cerebral concussion resulting from direct impact or whiplash is directly related to the amount of rotational acceleration of the head.

Cardiovascular effects following a head injury are closely related to the occurrence of concussion, studies with laboratory animals have demonstrated. This response is important also in predicting whether or not a head injury will prove fatal. Physicians are studying the relationship between these cardiovascular effects and sequelae of trauma to the nervous system.

Findings from these and similar studies are providing researchers with greater understanding of what actually happens during a head injury, and will enable them, in collaboration with engineers, to design more effective protective devices. Knowledge of exactly what happens to the brain after injury, when further severe brain damage may occur, will permit physicians to initiate treatment to limit brain injury to the irreversible damage occurring at the moment of impact.

In addition to the work under way in these areas, under the direction of the Surgical Neurology Branch, the Institute is also supporting a number of studies at medical institutions throughout the country, under the direction of its Section on Head Injury, Collaborative and Field Research. These include planning grants for four head injury clinical research centers.

Studies of the immediate events producing injury are providing researchers with information necessary to develop a mathematical model of head injury. Mathematical expression of the forces which cause various types of head injury in experimental animals should permit investigators to extrapolate this data from lower animals to man. Knowledge of the exact forces which produce head injury in man and the prediction of levels of tolerance to brain injury is requisite for the most effective design of protective devices--such as seat belts, helmets, head rests, and collapsible seat backs.

Studies of the immediate physiological and pathological effects of head injuries will be facilitated by an acute head injury service to be established at D.C. General Hospital in Washington, D.C. This affiliation with a local hospital will permit physicians to treat and study accident victims almost immediately after they have been injured. Other current projects are concerned with reaction to injury, both in experimental animals and in man. Clinical studies of electrolyte balance in humans and studies of blood flow and metabolism in animals are also being conducted.

Cerebrovascular Disease

Advances in instrumentation are enabling scientists to explore the fine details of cerebral blood flow, the most critical factor in stroke. Investigators at the Institute-supported Cerebrovascular Research Center at Bowman Gray School of Medicine reported this year on studies utilizing a new ultrasonic flowmeter which can be implanted in free-ranging animals. In the past, all studies of cerebral circulation, both in animals and man, have been done with the subject motionless and often under general anesthesia. The new device will provide a much better understanding of the moment-to-moment variations brought about by changes in activity.

The quest for useful drugs for treatment of cerebral embolism, one of the most common forms of stroke, has been furthered by Drs. Yihong Kong, Caetano Molinari, Robert Whalen, and Albert Heyman

at Duke University. They have found that intravenous injection of atropine in dogs can reverse the reduction in pulse rate, blood pressure, and cardiac output brought about by embolism, and have suggested possible use of the drug in humans for this purpose.

Surgeons are continuing to refine a new technique for thrombosing (closing off) cerebral aneurysms--ballooned weak spots in arterial walls within the brain--without opening the skull and manipulating brain tissue and blood vessels. Drs. John Alksne, Aaron Fingerhut, and Robert Rand at UCLA have reported success in creating a thrombus in seven cases by injection of tiny iron particles into aneurysms and holding them in place by use of stereotactically placed magnets. The technique necessitates only a small burr hole in the skull and local anesthesia.

Advances have also been made in simplifying cerebral hypothermia, the cooling of tissue to slow circulation during surgery. Drs. Thor Sundt, John Nofzinger, and Francis Murphey of the University of Tennessee have been able to eliminate oxygenator, mechanical pump, conventional heat exchanger, and anticoagulants in successful experiments with dogs. Their technique involves collecting blood from a leg artery and replacing it intravenously with an equal volume of banked dog blood. They then mixed the collected blood with an equal volume of 5 percent glucose in water, cooled the mixture to 4° C., and then perfused it by means of a hand pump through a cannula in the distal left common carotid artery. As the perfusion progressed, they controlled venous pressure by slowly bleeding the animals through femoral arteries. Their results suggest that the method, after perfection, may offer brain surgeons a less cumbersome means of cooling a limited area and gaining vital working time in human patients.

At NINDB in Bethesda, increasing emphasis has been placed upon spinal cord vascular diseases, previously neglected as a cause of neurologic deficit. Drs. Giovanni Di Chiro, John Doppman, and Ayub Ommaya have reported development of better techniques for visualizing the arteries supplying the spinal cord, improved diagnosis of spinal cord vascular insufficiency, and successful therapy for this disorder.

Significant advances have also been reported during the year in better defining stroke proneness, in the study of the vascular anatomy of the brain, and in the evaluation of synthetic adhesives for possible treatment of aneurysms.

Epilepsy

An association between brain temperature elevation and a certain type of seizure has been demonstrated, and this finding has led to the development of a new therapeutic approach. Also, the effectiveness of a high fat diet for controlling seizures in another group of patients

has been further confirmed. These findings were reported by a team of researchers under the direction of Dr. Maitland Baldwin at the Institute's Bethesda laboratories.

A temperature-telemetering device implanted on the surface of the patient's brain membranes aided in determining the association between elevated brain temperature and the increased frequency of a certain form of seizures. It was also found that seizures in such patients could be completely controlled by cooling the patient's head while anticonvulsant medication is administered. Researchers are expanding these studies to elucidate the seizure-temperature relationship.

Another Institute study has confirmed the finding that a high fat diet can control seizures in children with frequent seizures that do not respond to anticonvulsant drugs. Further studies are under way to pinpoint the chemical basis of the diet's effectiveness, and it is already clear that high levels of fats in the blood plasma are closely associated with cessation of seizures.

Using computer automation, a method for reinforcing conditioning in patients with sensory-evoked seizures has been developed. Certain forms of light or sound may precipitate seizures in these patients. Dr. Francis M. Forster, at the Institute-supported epilepsy clinical research center at the University of Wisconsin, last year developed an effective deconditioning technique which ameliorates this form of seizure susceptibility. Because this desensitization is not permanent but must be periodically reinforced, Dr. Forster has devised a simplified method which permits patients to carry out the reconditioning procedure at home.

A new technique has been developed which more precisely locates the exact focus of seizures in the patient's brain. This method employs a combination of implanted thin wires (electrodes) deep in brain structures, and a computer analysis of electrical burst activity from the electrodes. From the computer data, physicians can determine which areas of the brain must be removed to halt seizures and avoid unnecessary loss of healthy brain function. Drs. Mary A. B. Brazier, Brain Research Institute, University of California at Los Angeles, and Frank Morrell, Stanford University, are responsible for extending use of this method to neurosurgeons.

Basic research on the mechanism of seizure-causation has led to several new findings. For example, this year Drs. David A. Prince, Stanford University, and B. Joe Wilder, University of Florida, demonstrated in cats a possible control mechanism for seizures. They found that the brain cells around a focus of epileptic activity are inactive. This interaction, known as "surround inhibition," persists in the cat brain during an artificially induced seizure, preventing the spread of seizure activity to other areas of the brain. The scientists interpreted their findings as indicative of a basic control mechanism in brain tissue.

In another basic study, Dr. Florry Proctor and other scientists at Stanford University found that freezing tiny portions of cat brain deep in the subcortex causes epileptic activity to develop both at the freeze site and in other brain areas connecting with the freeze site. Epilepsy-like activity also developed in the opposite side of the brain in the analogous location. These studies add to knowledge of fundamental mechanisms in epilepsy, eventually leading to improved treatment methods.

Parkinson's Disease

A theory, held for many years, that Parkinson's disease confers resistance to cancer was conclusively disproved this year by Drs. Margaret Hoehn and Melvin Yahr of Columbia University. In a 15-year study of the natural history of the disease in 802 patients, they found no evidence of resistance whatsoever, with malignant neoplasms occurring third in causes of death among Parkinson patients, following arteriosclerotic heart disease and bronchopneumonia.

Other findings from the study were that the relative mortality risk is less in men than in women, and that the death rate for all Parkinson patients is three times that of the general population of the same age, sex, and color. The Columbia scientists found no correlation between the rate of progression and age of onset, severe infection, positive family history, or other neurological disease. Nor did they find any evidence that modern treatment to relieve symptoms has prolonged life. These findings provide epidemiologists and other investigators with better statistics for planning future work.

An assessment of the role of surgery in Parkinson's disease was made by Dr. Benjamin Boshes of Northwestern University. He and his group cited studies indicating that in many patients surgery is done "at a price"--when tremor in one arm is reduced or eliminated, the opposite arm appears to progress faster in developing symptoms. They noted, however, that a limited number hold their gain. Their data indicate also that when surgery reduces the amplitude of parkinsonian tremor, it does not affect the frequency, which remains in the range of 5 to 7 cycles per second; that it does not affect the akinesia, or slowness of movement; and that even in unilateral lesions, there is a 25 percent reduction in voice power. Citing their earlier reports of losses in coordination and utilization of the limbs, the group stated that the surgical lesion removes an important neural relay, and that these patients must have intensive retraining to utilize substitute circuits.

Other important research approaches in Parkinson's disease involve studies of abnormalities of brain chemistry and of the anatomical, physiological, and pathological basis of the disease.

These studies have led to a new theory of movement control, envisaging a balance within the nervous system of two motor control pathways. The activity of one pathway is mediated through the biogenic amines; that of the other, through other compounds--acetylcholine and the enzyme cholinesterase. Parkinsonism occurs when there is an imbalance--a reduction in activity of the biogenic amine pathway. Symptoms may be alleviated either by accomplishing a corresponding reduction in activity in the acetylcholine-mediated system, through drugs, or possibly surgery, or by increasing the activity of the parallel amine pathway.

Interest has been aroused in the past year by reports of possible success in achieving this latter effect through treatment with large doses of the amine, L-DOPA. It is not yet known whether this compound will prove useful in therapy, but Institute-supported trials are under way at Columbia University.

Multiple Sclerosis

A degenerative neurological disease which resembles multiple sclerosis (MS) in some respects was passed by brain inoculation from infected chimpanzees to another group of chimps this past year. Later the disease was passed to a third generation, and the incubation period was shortened to a year or less. Last year, Institute investigators had transmitted the disease (kuru) by some infectious agent from man to animal. Although efforts to filter the infective agent have failed thus far, Institute scientists believe they are dealing with a virus. Some scientists believe that this research has strengthened the theory that MS may be caused by a virus.

In another research approach to MS, viruses also may be implicated, since they are thought to trigger an autoimmune process which is a disturbance in the body's immunological defense system. Scientists have now found evidence that circulating blood cells (lymphocytes) may play an essential role in the autoimmune process since they produce most antibodies. In one study, it was found that the alteration of immune function which occurs in MS may be mediated by lymphocytes that are sensitized against nerve tissue. In the same study, animals deprived of lymphocytes by neonatal thymectomy did not develop demyelinating disease.

This research has been done only with cell cultures of animal nerve tissue that were infected with an experimental form of demyelinating disease. However, it suggests that MS might be combated or even prevented in man without using agents that suppress lymphocytes indiscriminately, leaving the body open to infection.

A metabolic defect in patients with MS is suspected by Northwestern University medical researchers following a 5-year study. The research included a study of biochemical processes in the brains

of chicken embryos, a review of autopsy results, and a survey of world statistics on MS. Their experiments on brain development in chick embryos show that polyunsaturated fatty acids from fish and vegetable oils are necessary for normal brain development. One of these, a substance called linolenic acid which is more prevalent in the brain than other organs, comes principally from fish and seed oils. In tropical as well as certain Asiatic countries where diets are rich in seafoods, soybeans, millet, and vegetable oils, MS is rare.

Diseases of the Neuromuscular System

Germine diacetate has been found effective in treating myasthenia gravis (MG) patients who cannot be helped with anticholinesterase medication. The research was conducted by grantees at Harvard Medical School.

The improvement in skeletal-muscle power of all of the diseased muscles--bulbar, trunkal, and appendicular--was found to be significant with the drug. The greatest improvement in function occurred in the ocular muscle, which has been most difficult to control with other drugs. Germine diacetate was effective orally as well as by the intravenous route, and no side effects that would represent an obstacle to its clinical usefulness were seen. The margin of safety of this alkaloid derivative of the veratrum plant appeared to be broader than that of anticholinesterase agents.

In a related study, a team of physicians led by Dr. Kermit E. Osserman, Mount Sinai Hospital, New York, have demonstrated the effectiveness of short, intensive corticotropin therapy in patients with severe, generalized MG. These patients showed a striking improvement when treated with short-term courses of massive dosage corticotropin.

During the course of therapy, a brief intensification of MG symptoms was noted in most patients; this was followed by improvement. Both the worsening and subsequent improvement appeared proportional to symptom intensity that occurred prior to treatment. Smaller doses of the hormone were less effective, and no serious side effects were observed after repeated courses. Duration of improvement has averaged 3 to 4 months to date, and one patient is still improved 8 months after the last course of treatment.

Dystonia musculorum deformans (DMD), a disorder of movement, may be inherited in either an autosomal dominant or recessive form, according to an Institute study of 65 families involving some 400 persons. This disorder begins in childhood with unexplained turning of the foot or irregular jerking of the hand. The finding is of immediate importance to physicians engaged in genetic counseling of DMD patients and their families.

A method for the large-scale purification of acetylcholinesterase (ACH-ase), an enzyme of great importance in the conduction of nerve and muscle electrical impulses, has been developed by Institute-supported scientists at Columbia University. In spite of the recent advances of knowledge in protein chemistry and the role of large chemical molecules in cell functioning, very little is known about the chemical composition of ACh-ase, because there has been no technique available for preparing the pure enzyme in amounts large enough for analysis. The investigators extracted the enzyme from fresh tissue of the main electric organ of the electric eel. They found ACh-ase to have a molecular weight of 250,000, including 18 amino acids and 3 amino sugars. They noted that the large ACh-ase molecule is probably a polymer formed by subunits, and indicated that studies are in progress to test this theory.

Two disorders characterized by muscle rigidity have been found to be identical. They are paramyotonia congenita (PC) and hyperkalemic periodic paralysis (HPP). The research was conducted by a team of Institute-supported researchers at the Neurological Institute, Columbia-Presbyterian Medical Center.

Using a battery of clinical tests, the neurologists found unequivocal signs of myotonia in 35 members of four families affected by the two disorders. In some individuals, clinical features of myotonia were predominant, while in others--often in the same family--those of periodic paralysis were most evident. Thus, the investigators concluded, myotonia appears to be the minimal expression of the genetic trait in those families. The presence or absence of associated HPP, and the severity of either myotonia or periodic paralysis, appeared to be independently variable. The researchers noted that such a large variability in the expression of a genetic trait is typical of the type of inheritance pattern of both HPP and PC (autosomal dominant inheritance). This genetic pattern was found in all four families. The study also suggested that a defect in permeability properties of the excitable membrane of voluntary muscle is responsible for the syndrome.

A genetic protein defect which is specific for patients with progressive muscular dystrophy (PMD) has been discovered by a scientist in the Department of Neurology, Warsaw Medical Academy, Poland. The study is using counterpart funds and has been developed in cooperation with the Institute's Bethesda laboratories.

The defect is an abnormality of the beta$_1$-globulin fraction of blood serum. This abnormal globulin was found in a large majority of patients with PMD and in their carrier mothers, but not in patients with other forms of muscular dystrophy or other neuromuscular diseases. The finding suggests that there is an inherited protein abnormality specific for progressive muscular dystrophy. Hope for the eventual development of preventive measures for this crippling disease is advanced by this discovery.

Scientists at the Institute's Bethesda laboratories have discovered two new types of neuromuscular disease: a familial disorder consisting of loss of muscle fiber striations with progressive weakness; and complete atrophy of type I muscle fibers, associated with congenital weakness fatal at 18 months. These studies, along with extensive chemical study of muscle, have resulted in clarification of some of the causes of muscle weakness. Further clarification can be expected from these continuing studies which correlate muscle pathology with specific histochemical reactions.

Hearing and Speech

New techniques in hearing testing will make possible diagnosis of hearing loss and initiation of appropriate therapy in very young children, at an age when language training is most successful. Evoked response audiometry, a valuable new research tool, can be used to accurately evaluate hearing ability in newborns, mentally retarded, or brain-damaged children, and others unwilling or unable to cooperate. Current audiometry techniques often cannot detect hearing loss in children under 5 or in other difficult cases.

A new technique, developed this year, should shorten the time needed to prepare stained specimens of temporal bones for study from several months to only a few hours. Scientists using this technique can increase the number of specimens available for immediate study and reduce the chances of chemical and structural changes in the bones during preparation by the older, longer process.

Successful removal and reimplantation of the larynx in experimental animals is providing knowledge of the basic mechanisms involved in laryngeal transplantations. This work aims at eventual development of an artificial larynx which would benefit laryngectomy and accident patients.

Kernicterus may cause damage to the nerve pathway from the ear to the brain, an Institute-supported investigator reports. It had been believed that this disorder--which sometimes develops in newborns who have jaundice--caused damage to the inner ear, resulting in hearing disabilities. The finding that the damage in kernicterus may be central rather than peripheral can result in more effective clinical management of children with kernicterus-induced deafness, while also providing scientists with essential knowledge of central hearing damage.

Basic studies of the inner ear are providing better understanding of the structure and function of the inner ear and of the processes of disease production and prevention. One study of the vestibular system, which controls balance, has given researchers new knowledge of the biochemistry of the fluids of that organ (the

labyrinth) and of the pathology of ossification there and in the cochlea. Other studies have advanced our understanding of the central vestibular connections and of the processes of dizziness.

Many persons who cannot be helped by hearing aids are still being fitted with them, Institute-supported studies show. In other cases, many are being sold aids which are not right for their hearing disabilities, and many persons with undiagnosed ear diseases that could be helped or cured are experimenting with a variety of inadequate hearing aids until their diseases pass beyond the remediable stage. The Institute is supporting studies of hearing aids and their suitability in specific types of deafness; and NINDB scientists emphasize the importance of thorough otologic examinations before any remedial steps--particularly hearing-aid acquisition--are taken.

Brain Tumors

The most promising recent advances in brain tumor research have come in the area of diagnosis. In the past 10 years, new radioisotopes have been developed and equipment for brain scanning perfected. Another method for diagnosing brain tumors involves lipid (fat) metabolism. Researchers have found desmosterol (a forerunner of cholesterol) accumulates in tumor tissue but not in normal brain tissue. Development of a rapid test to detect desmosterol offers a potentially useful method for diagnosing brain tumors.

Differentiation between malignant and benign tumors may be possible with a new enzyme technique developed by Institute grantees at the Copenhagen Neurochemical Institute, under the direction of Dr. W. Gerhardt. Changes in the ratios of five distinct forms of a certain enzyme normally produced by the body's cells enable investigators to determine whether or not a tumor is malignant. This test method is easily learned, inexpensive, and so rapid that diagnosis of a malignancy can be made an hour after sampling. Knowledge of whether a tumor of the brain is benign or malignant aids the physician in selecting the most appropriate treatment methods.

In the area of treatment research, NINDB and National Cancer Institute researchers have initiated a pilot cooperative study of medications. Studies are under way to determine the value of mithromycin, the first drug to be tested, in treating brain tumors. Another study concerns the effects of low temperature (hypothermia) on the brain. This technique's possible treatment potential is in addition to its known usefulness during brain surgery.

Highlights of Research Progress
during 1967

on

ALLERGY - IMMUNOLOGY

Research supported by this Institute produced a number of advances in the fields of allergy and immunology during 1967. Investigations have been directed toward solving the problems of organ transplant rejection, developing techniques for studies at the cellular level, producing animal models which can simulate autoimmune diseases in man, understanding the processes involved in the immunity to infections, and seeking new methods for treating allergic disorders.

Immunology and Organ Transplants

Great strides have been made toward matching tissues of donors and recipients of organ transplants much as red blood cells are matched for blood transfusions. A number of histocompatibility antigens in white blood cells which appear to be important in determining whether the body will accept or reject a graft have been identified. (Antigens are substances foreign to the body; antibodies are the substances produced by the body to counteract antigens.) Typing techniques developed by Institute contractors are currently being evaluated in five medical institutions for the selection of donors and recipients of kidney transplants. Early results indicate that proper matching before transplantation may be the best way to select donor-recipient pairs so a minimum immune rejection response will be evoked.

While tissue matching will reduce the body's transplantation rejection response, all conflict between tissues probably cannot be eliminated. An important part of current research is therefore aimed at suppressing the response to the remaining conflicting elements. Institute grantees have found that antisera prepared against lymphocytes (white blood cells used by the body for defense) markedly reduce the tissue rejection phenomena encountered with organ transplants, but have relatively little effect on other kinds of immune reactions. Furthermore, toxic effects of these antisera appear to be less than those seen with other suppressive agents. The most commonly used methods of suppression up to now have included the administration of steroids, antimetabolites, and X-ray, all of which interfere with the entire immune capability of the body. Thus, while the body's rejection of the organ transplant is decreased, so also is its ability to combat infections.

Progress toward purification of transplantation antigens from guinea pigs has been made and it seems reasonable that this information will be

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applicable to the same materials from human tissues. The ultimate goal in organ transplantation is to persuade the recipient to accept a transplant without interfering with his other immune responses. Identifying specific antigens involved in transplant rejection could attain this goal, because it is possible experimentally to block the body's response to a specific antigen by giving large doses of that particular antigen, while the recipient's capability to respond to other substances remains unchanged.

Basic Studies

The mechanism of cellular hypersensitivity--the phenomenon generally accepted as responsible for organ transplant rejection and many autoimmune diseases--is poorly understood. For years, it has been possible to transfer cellular hypersensitivity in man using extracts of immune cells. During the past year, the guinea pig and rabbit have been adapted as laboratory models. The availability of these models should hasten research progress.

It has long been thought that cellular hypersensitivity is produced by specific products from the lymphoid cells; and grantees at four institutions are obtaining broadly similar information, although they are using different models, techniques and criteria. Lymphocytes from sensitized individuals respond to specific antigen in tissue culture by producing a substance, identified as a low-molecular-weight protein, which can duplicate the action of the original lymphocyte. This substance is distinguishable from presently known antibodies; and of special significance, it causes normal lymphocytes in tissue culture to respond like sensitized cells. These investigations on basic principles underlying cellular hypersensitivity could lead to its control, and provide a means for solving the practical problems of transplantation, tumor immunity, and autoimmune disease.

A discovery made by an Institute grantee at Trudeau Institute, Saranac Lake, New York, was that antibacterial immunity requires the collaboration of two cell types. Using new techniques for study of cells in the laboratory he found that a lymphoid cell causes increased sensitivity to the invading microorganism or its chemical products, so that a scavenger cell, called a macrophage, can become hyperactive and devour the bacteria. This increased killing capacity of the macrophage occurs only when the hypersensitivity is present.

A model which represents a major accomplishment long sought by immunologists has been developed by grantees at the Scripps Clinic and Research Foundation, San Diego, California. This model, an efficient tissue culture system in which the immune response can be studied entirely in the test tube, permits continuous observation and analysis of all the reacting tissue, which has not been possible in the body.

Other notable advances have been made in developing and perfecting techniques necessary for immunological studies in the Institute's intramural laboratories. A method for detecting and counting antibody-forming cells in the test tube, the hemolytic plaque technique, has now been expanded to apply to all the major categories of antigens. A related technique concerns the use of the ability of antigen-coated bentonite (aluminum silicate) particles to adhere specifically to the surface of immune lymphoid cells, making possible the detection of these cells using a variety of antigens.

A fourth class of immunoglobulins, the proteins which carry the antibody activity in the blood, has been demonstrated by a grantee at Children's Asthma Research Institute, Denver, Colorado. Designated IgE (for immunoglobulin E), this new immunoglobulin class has been associated with ragweed allergy; three classes of immunoglobulins, IgG, IgM, and IgA have been previously identified.

Research at the Institute's Rocky Mountain Laboratory in Hamilton, Montana, has made it apparent that enzyme-fragmented antigens are still antigenic, and in many instances possess new antigenic factors not found on the surface of the whole antigen. This research, directed toward finding the difference between allergic reactions mediated by antibodies and those mediated by cells, has been concerned with the effect of enzyme-fragmented antigens on the type of hypersensitivity and antibody developed in animals.

Grantees of this Institute and of the Institute of Arthritis and Metabolic Diseases at the Johns Hopkins University and Rockefeller University isolated a second highly purified antigen from ragweed pollen and designated it antigen K. Earlier work had resulted in the isolation of antigen E. Such materials, if appropriately administered to allergic individuals, can reduce their sensitivity, and it is thought that the availability of antigen K should improve the prospects for such therapy.

Useful animal models for the study of serious human autoimmune diseases were reported. Guinea pigs, specially sensitized by the injection of thymus or muscle material, develop a disease somewhat similar to human myasthenia gravis, thus providing a potential method of studying this disease. Rhesus monkeys, injected with brain tissue to produce autoimmune encephalomyelitis, develop disorders which have similarities to multiple sclerosis. A wide range of acute and chronic forms of autoimmune encephalomyelitis has been produced in both monkeys and guinea pigs. Using these models, new information has been obtained on genetic and cellular factors controlling these reactions and on the importance of cellular hypersensitivity in autoimmune diseases. Since many neurological responses seen in man can be studied in the monkey, this animal should prove especially helpful in the study of the pathogenesis of diseases similar to multiple sclerosis.

## VIRAL DISEASES

Viral infections constitute the largest single disease entity afflicting every generation of mankind. Viruses can kill or deform an unborn child, can cause croup, influenza, and pneumonia in infants and such childhood diseases as polio, mumps, measles, and chicken pox. They trigger encephalitis, gastrointestinal disorders, cold sores, colds, and are thought to contribute to chronic and degenerative diseases such as emphysema and chronic bronchitis. The following accomplishments are examples of the Institute's efforts in attacking and hopefully conquering viral diseases.

### Rubella

Prospects are encouraging for preventing the next anticipated Rubella (German Measles) epidemic of the early 1970's with a safe, effective vaccine. Within two years after scientists in the Division of Biologics Standards had developed a live attenuated rubella vaccine (HPV-77), these results were announced at an NIAID contractors' meeting: (1) of the 500 vaccinees who received various strains of the experimental vaccine, 96% had developed antibodies against the virus; and (2) there was no evidence of disease or transmission of the virus to susceptible contacts, although in some cases virus was shed from the nose and throat of those inoculated with HPV-77 and other similar rubella virus strains. Further testing is being conducted by NIAID contractors and other scientific teams.

### Respiratory Syncytial (RS) Virus Disease

A new concept of the interaction of RS virus and antibody offers an exciting possibility for solving one of the most pressing needs in respiratory disease control. In fact, it may alter much of the current thinking in the development of other respiratory virus vaccines.

RS virus--which hits heaviest during the first six months of life and causes almost half of the 10,000 infant deaths each year from pneumonia--has been the subject of an intensive, but discouraging vaccine development effort for some time. Now it has been found that the seemingly protective antibodies transmitted from the mother to her unborn child aggravates the seriousness of illness in RS virus infections in infants presumably by reacting with the virus to damage the lungs. Scientists from the NIAID and Children's Hospital in Washington, D. C., who reported these findings, point out that the higher the antibody level in the baby's blood stream, the greater the potential for severe pneumonia when infections with RS virus occur.

It has now been postulated that a live attenuated respiratory virus vaccine is probably safest for young children since it would cause a mild, relatively harmless infection which stimulates their own antibody production. One such vaccine--a low temperature adapted strain of RS virus--is under development in an NIAID laboratory. After being passed 16 times at 26°C through bovine embryonic kidney tissue, this strain ($A_2$) shows reduced infectivity and virulence in adult volunteers. Tests in successively younger subjects are currently being sought preliminary to tests in infants.

Research efforts have been hampered by low yield of RS virus in culture fluid and by loss of as much as 80 to 90 percent of infectivity during the virus isolation process. A promising report--by NIAID and Oak Ridge National Laboratory investigators--indicates that it will now be possible to collect and concentrate adequate amounts of RS virus for further vaccine studies. The use of sophisticated techniques of high-speed centrifugation and density banding prevents inactivation of the virus.

Parainfluenza

A significant finding in the search for effective parainfluenza virus vaccines was made by NIAID scientists working with others at Georgetown University School of Medicine. In their studies with adult volunteers, they found that live type 1 parainfluenza virus was more effective in stimulating antibody response in respiratory tract secretions than was administration of inactivated (killed virus) vaccines. It is also interesting that the live virus vaccine was administered by nasal spray while the inactive vaccine was given by injection beneath the skin of volunteers.

Further, virus-neutralizing antibody was found in association with immunoglobulin-A in nasal secretions, opening up new possibilities for detecting antibody presence through immunoglobulin-A determination.

Although early tests on killed vaccines to protect against parainfluenza virus types 1, 2, and 3 showed them to be nearly 100 percent effective in stimulating an acceptable rise in the level of protective antibody in the blood stream in young infants, there was only limited effedtiveness against the natural illness. This failure, thought to be due to the failure to stimulate local antibody in the respiratory tract, has given added impetus to the live virus studies.

Other NIAID laboratory studies have shown that infection with adenovirus or immunization with soluble antigens resulted in immunoglobulin responses similar to those found in the parainfluenza work. Neutralizing antibody of both the immunoglobulin-G and immunoglobulin-M types occurred, with the former persisting for up to 50 weeks. And clinical studies with $A_2$ influenza virus indicated that antibodies in external secretions (particularly nasal wash antibodies) were not just a reflection of serum immunoglobulin and antibody content. In infected individuals, high concentration of immunoglobulin-A antibody was found in nasal wash but not in the serum. This also emphasized the importance of respiratory secretion antibody response to infection and the need for live virus vaccines.

Poliomyelitis

Reports continue to come in on the effectiveness of polio vaccines. In a recent study completed by NIAID grantees at Boston University, blood specimens of 2,500 polio vaccine recipients were tested for susceptibility to the disease. Their results showed a high degree of protection against poliovirus types 1, 2, and 3 at all age levels. The lowest protection was found in pre-school children and against type 3.

Measles (Rubeola)

For the first time in 55 years, reported cases of measles (rubeola) in the United States in 1967, dropped below 100 per 100,000 population. In 1967, the case rate per 100,000 population was 37.4 as compared to 104.2 the previous year.

This, of course, is directly attributable to the availability of vaccines and points up the effectiveness of the nationwide measles vaccine program. Although reports of reactions from the inactivated vaccine have been relatively low, some studies (including those supported by NIAID at the University of Colorado) indicate that those receiving the killed vaccine sometimes develop "atypical measles" or a severe local reaction if they later receive the live virus vaccine or are exposed to the natural disease. (The killed vaccine is generally not given to healthy children but rather to those undergoing treatment with immunosuppressive drugs.)

Infectious Hepatitis

A preliminary but important assist in the study of infectious hepatitis came with recent reports of successful transmission of the disease from man to marmoset. With a marmoset colony now established at a Maryland laboratory under contract to NIAID, studies are proceeding using the blood specimens of heart surgery patients. Because of the number of blood transfusions they receive, such persons often are particularly likely to develop hepatitis.

Other Enteroviral Infections

HFM--a recently identified disease syndrome of the hands, feet, and mouth--has been reported by NIAID grantees at Emory University, following an outbreak in Atlanta, Georgia. Of 30 children with symptoms, 19 were found to harbor the Coxsackievirus A16 as were seven apparently healthy family members. Four other patients were found to have herpes simplex virus, and both viruses were isolated from one patient. The investigators suggest that the HFM syndrome appears to conform to certain other enteroviral infections where more than one enterovirus is related to the same set of symptoms. The most difficult entity to differentiate from HFM was herpes simplex infection, particularly when skin lesions appeared to be absent. Only after thorough examination of areas usually not minutely inspected (the palms or between the fingers and toes) were such lesions found.

ECHO virus infection may cause more cardiovascular involvement than is usually clinically recognized, according to NIAID grantees at New York University. Recently, on postmortem examination of a patient whose death had been confirmed as due to myocarditis (inflammation of the muscular walls of the heart), ECHO virus was found only in the heart and in no other tissues. It has been suggested that such a diagnosis might sometimes be overlooked due partially to lack of characteristic virus involvement in other organs.

Other Respiratory Diseases

Reoviruses--generally thought to cause only a mild respiratory infection--have now been implicated in a fatal case of interstitial nonbacterial pneumonia associated with a skin rash and infection of the upper respiratory tract. This first report of a skin reaction and first isolation of a reovirus type 3 from a human lung was reported by NIAID supported grantees at Wayne State University and Detroit General Hospital. Pathogenic bacteria were not cultured from the patient's nose, throat, sputum, blood, or lung at autopsy. However, widespread infection with reovirus type 3 was evident and pathologic tissue abnormalities were found only in the lung.

Enthusiastic reports continue from the military services on the effectiveness of the oral Adenovirus-4 vaccine developed by NIAID. Nearly half a million U. S. Army, Navy, and Marine combat trainees have received the live enteric-coated pill which does not dissolve and begin its antibody-stimulating activity until it reaches the intestines. Administered at the first sign of an outbreak, the vaccine within two weeks virtually halted the epidemic-spread of adenovirus-associated respiratory disease in a military recruit population. Hospitalizations for serious respiratory infections were reduced by more than 60% at some of the training stations.

One of the obstacles in development of a vaccine against the 100 or more rhinoviruses implicated in the common cold has been the problem of determining exactly which viruses cause the majority of illnesses. Important leads in this aspect of rhinovirus vaccine research have been provided by scientists at the University of Washington who report a very broad, heretofore unsuspected antigenic relationship between many of these rhinoviruses. They postulate that there is some "group" antigen in rhinoviruses and some stimulation of cross-immunity within each group. If this proves true, it could open the way to development of a vaccine--using only 4 or 5 groups of viruses--which would be effective against all of the rhinoviruses.

Another advance in the effort to conquer the common cold was made in the laboratories of NIAID recently where six previously unrecognized

viruses were isolated from nasopharyngeal washings from NIH employees suffering cold symptoms. The viruses, resembling avian infectious bronchitis virus (IBV), were recovered by use of a newly developed organ culture technique after standard tissue culture techniques had failed to yield any viruses. Two of the viruses were similar to strains 229E (found by NIAID grantees at the University of Chicago) and B814 (which in England has been demonstrated to produce colds in volunteers). Although the six viruses have not been proved to be the cause of the NIH employees' illnesses, their close resemblence to strain B814 lead NIAID investigators to suspect that--at least in certain cases--they can be responsible for common cold symptoms in adults. All of the new "IBV-like" viruses were recovered during the months of December through March when the usual tissue culture techniques were unsuccessful in growing viruses from patients with colds.

Chronic and Degenerative Diseases

The role of viruses in chronic and degenerative diseases continues to evoke increased interest as incriminating evidence mounts.

One of the characteristics of multiple sclerosis in humans is demyelinization (destruction of a fatlike sheath around certain nerve fibers) in the brain and spinal cord. Scientist-grantees at Rockefeller University have found that a cause of a demyelinating disease in sheep --visna virus--can be grown in sheep choroid plexus tissue cultures. When these cultures are overlaid with baby hamster kidney tissue culture cells, the hamster cells degenerate even though no virus growth can be demonstrated in them. The investigators suggest that this degenerative process is caused by cell membrane impairment, which might be the mechanism for the demyelinization in the intact nervous system.

With increased knowledge of Aleutian Disease of mink has come hope for further understanding of possible similarities in human kidney disease. Aleutian Disease had been thought to be of viral origin until an NIAID grantee at the University of Connecticut produced evidence suggesting that the infecting agent may be smaller than any known virus. Now grantees at Washington State University have described the development of kidney glomerular lesions in mink suffering Aleutian Disease, lesions closely resembling some of those seen in certain experimental and spontaneous diseases of animals and humans. In eclampsia and pre-eclampsia, it has been felt that intravascular coagulation and the subsequent depositing of fibrin--an elastic protein which forms the essential portion of a blood clot--leads to glomerular destruction. In mink with Aleutian disease, the Washington State scientists found that changes indicated coagulation had occurred within the blood vessels of the glomeruli (thin membranes and capillary walls of the kidney) as the condition progressed. They suspect that the deposition of fibrin or incompletely polymerized fibrin as a result of virus-antibody combinations is the mechanism setting off glomerular damage.

The glomeruli may be a promising site for finding antibodies in certain virus infections which have previously appeared to be lacking in antibody response. This was suggested by NIAID grantee scientists at Scripps Clinic and Research Foundation following studies of lymphocytic choriomeningitis (LCM) virus in neonatally infected mice and those born of infected mothers. These LCM-"tolerant" carriers showed gamma globulin and beta 1C globulin (which were in part antibody to LCM virus) concentrated in the glomeruli and absent from other tissue sites.

"Slow" virus diseases share many of the distinguishing characteristics of chornic and degenerative diseases and are of prime concern to NIAID's Rocky Mountain Laboratory in Montana. The virus causing scrapie in sheep --similar in its manifestations to certain neurologic disorders in humans--was found to be limited to the lymphatic system during the second and early part of the third year when subcutaneously inoculated into goats which remained free of illness. At 32 months, it first appeared in the brain and spinal cord of a clinically normal goat. Virus was also recovered from the brain of a goat in which clinical scrapie appeared at 35 months, but was not recovered from any tissue which would contribute to environmental contamination.

Antiviral Substances

With the knowledge being amassed on antiviral substances, one NIAID grantee at Stanford University Medical School has forecast that science is on the threshold of an era that may see chemotherapeutic and other nonimmunologic methods for control of human viral infections become as commonplace as are the present day use of antibiotics in treating bacterial infections. The most promising antiviral agent is interferon.

At Stanford University, a heavy interferon was produced by injecting statolon (a derivative of Penicillium stoloniferum) into chickens. Later a lighter type was seen which was indistinguishable from virus-induced interferon.

Other investigations--by the Stanford group and grantees at the Medical College of Virginia--showed that a synthetic plastic, pyran copolymer, appeared to be a potent stimulator of interferon production in man and experimental animals.

As the result of experiments performed by NIAID scientists, it has been suggested that the maintenance of stable antiviral activity in the presence of interferon could be the result of continued induction by interferon of enough new antiviral protein to replace decaying antiviral protein. They concluded that several factors affect the interferon-induced resistance to viruses in tissue culture. There is a rapidly increasing antiviral activity for about the first seven hours of cell-interferon reaction. Thereafter, antiviral activity remains relatively stable so long as there is an unchanging amount of interferon

in the fluid surrounding the cell. Continued presence of the initial concentration of interferon was needed to maintain the established level of resistance. The addition of more interferon resulted in a further rise of resistance, with the level of cellular antiviral activity being determined mainly by the concentration of interferon rather than by the amount applied.

NIAID grantees at Presbyterian-St. Luke's Hospital in Chicago --studying the interrelationship of mumps virus and host cells--report that mumps virus attenuated by passages in avian tissues induce 10 to 100 times more interferon in animal cells than do virulent strains of mumps virus.

An explanation for the persistent virus infection in children with congenital rubella may have been found by NIAID grantees at Baylor University. In their recent study of a group of children so afflicted, they report that rubella infection early in pregnancy may not elicit an interferon response, thus permitting the establishment of a virus-cell relationship which is not lethal to either.

Tumor-causing (oncogenic) viruses

Adenovirus 2--which infects most children before age 1 and which was formerly considered nononcogenic--has been demonstrated to transform rat embryo cells. Based on these studies--supported by NIAID and the National Cancer Institute--it has been suggested that adenoviruses 1, 2, and 5 be characterized as an oncogenic subgroup, and that human tumors should be tested for the possible presence of 11 adenoviruses which have proved or suspected oncogenic activity in animals.

## BACTERIAL DISEASES

Once considered doomed by the "miracle sulfa drugs" and antibiotics, bacterial diseases have reasserted their serious threat to health.

Many bacteria have become resistant to antibiotics previously effective in their control. Infections with resistant gram-negative bacteria, in particular, are increasing. The mode of action of many antibiotics is still incompletely understood; and the significance of "L"-forms--bacterial forms lacking a cell wall which often develop under antibiotic influence--remains to be established.

The NIAID places continuing emphasis on the problem areas. Almost one-third of the research projects in infectious diseases supported by Institute grants last year were aimed at solving problems in bacterial diseases.

Streptococci

Streptococcal infections remain a major cause of illness, and their sequelae--rheumatic fever, rheumatic heart disease, and the kidney disease glomerulonephritis--have been long recognized as causes of death or chronic illness. At present, preventive therapy with antibiotics is the only weapon available against recurrence of the serious sequelae.

A promising development last year was the purification and testing of a relatively non-toxic, M protein (antigen) component of group A streptococci as an immunizing agent by grantees at the University of Chicago. They conducted small-scale trials with the M protein vaccine in which children produced antibodies capable of destroying streptococci. None had any unfavorable reactions to the experimental vaccine. Because of the problem of producing hypersensitivity--thought to be a factor in streptococcal sequelae--work toward a practical vaccine proceeds cautiously. Studies on immunization and the immune response are being undertaken by the Institute in collaboration with the Chicago investigators.

A further possible complication to the development of a vaccine is the finding by grantees at Western Reserve University that antibodies to certain components of streptococcal cell walls react with human heart tissue.

The search for animal model systems for the study of the sequelae of streptococcal infections was continued. A Stanford University grantee, studying the M protein of group A streptococci, has produced kidney tissue changes in rats, resembling true glomerulonephritis. At the University of North Carolina, a grantee is studying a mouse model of rheumatic-like carditis (heart inflammation). In these mice, lesions similar to those found in human rheumatic fever were produced by sterile extract of disrupted streptococcal cells and by cell fragments, but not by the interior portion of the bacteria without the cell wall.

Grantees at Western Reserve University and the University of North Carolina are studying the fate of streptococci and their cell walls in animals. Laboratory procedures have shown that antigenic fragments persist in the tissues considerably longer than intact (whole) streptococci. Chronic lesions have been associated with the presence of group A streptococcal cell wall material. By contrast, only acute localized tissue-destroying reactions are produced by group D streptococci, which are rapidly eliminated from the body --apparently because of their susceptibility to lysozyme, a body protein with antibacterial action. Group A cells are completely resistant to lysozyme.

Staphylococci

Staphylococcal diseases continue to cause trouble. The organisms may persist in the tissues for a long time and often drug-resistant strains emerge during extended antibiotic treatment. Some new findings, however, have been made.

Workers at the Medical College of Georgia reported progress in finding ways of eliminating Staphylococcus aureus from the nasal passages of human carriers. Treatment with lysostaphin, an enzyme which attacks the cell wall of some bacteria, selectively reduced the number of dangerous coagulase positive staphylococci, and apparently allowed overgrowth by the harmless bacteria normally found in the nose, which interfered with later reacquisition of the disease-causing strains of staphylococci.

Staphylococcal endocarditis, inflammation of the lining of the heart and its valves, frequently presents an overwhelming challenge to antibiotic treatment. Grantees at the University of Cincinnati, using their experimental canine model of acute endocarditis, have contributed new data on drug levels and length of treatment which may be of aid in curing human cases of the disease.

Antibacterial Substances

Institute scientists have found that in the test tube a naturally-occurring protein, plasma siderophilin, can affect the metabolism and growth of some bacteria, such as Staphylococcus aureus. In the animal body, it may function as a non-specific factor in resistance to bacterial infection. A similar protein found in human secretions, called ekkrinosiderophilin, apparently also slows the growth of staphylococci by binding iron otherwise available to the bacteria. New methods for isolating and purifying this protein from human milk have been developed in the past year in cooperation with scientists of the National Institute of Arthritis and Metabolic Diseases.

Other Institute scientists have obtained promising results in mice by modifying agents which have known or potential antimicrobial activity. They have altered some with additives to enhance their action and changed others chemically to reduce toxicity.

Progress in the battle against some bacterial drug resistance has also been reported. In some diseases, a combination of drugs is more effective than a single drug. This effect, called synergism, gives a greater combined action than the sum of the individual actions of the drugs. Grantees at Harvard Medical School and Thorndike Memorial Laboratory showed that combination of penicillins--one to inhibit penicillinase (the enzyme produced by bacteria to destroy penicillin),

the other to attack the bacteria directly--produced a favorable response when used to treat some patients with urinary tract infections.

Conversely, the increasing use of combinations of agents can produce such problems as antagonism--interference by one drug with the action of another when the two are used in concert to combat infection. Working with dogs, grantees at the University of Washington found an example of this phenomenon when pneumococcal meningitis was first treated with the bacteriostatic (growth-slowing) drug chloramphenicol and then by penicillin, the action of which is bactericidal (killing). It appears that interference may be of clinical importance primarily in situations where early, rapid killing of bacteria is essential for recovery.

Gram-Negative Bacteria

Infections resulting from gram-negative rod-shaped bacteria continue to pose serious problems because of the frequent resistance of these bacteria to one or more antibiotics.

Grantees at Wayne State University and Detroit General Hospital, for example, reported a survey of 82 patients with pneumonias caused by gram-negative bacteria. The study indicated that certain bacteria, such as Escherichia coli, though abundant in the normal human intestine may be responsible for a constant incidence of dangerous pneumonias. This seems especially true in older persons already suffering from a chronic disease. Such pneumonias are difficult to diagnose, are hard to treat because of drug-resistance rapidly acquired by causative organisms, and are often fatal. The organisms implicated in these illnesses include Pseudomonas, Bacteroides, Proteus, Haemophilus, Achromobacter, and Klebsiella-Enterobacter.

Cholera is another example of a gram-negative bacterial infection being studied by the Institute, in which research gains for successful treatment have been made, but effective preventive methods are elusive. The SEATO-Cholera Research Program, and the scientific direction of the Pakistan-SEATO Cholera Research Laboratory at Dacca, East Pakistan, continues to be a responsibility of the NIAID Director of Intramural Research, as Chairman of the NIH Cholera Committee.

Dr. Robert Allan Phillips, Cholera Research Laboratory Director, received the 1967 Albert Lasker Clinical Research Award for his studies on maintenance of water, electrolyte and acid-base balance in cholera patients and the development of a simple, life-saving cholera treatment which has reduced the death rate in patients with the disease from 60 percent to less than 1 percent.

Studies at the East Pakistan laboratory recently have shown that the standard United States cholera vaccine provides 85 percent protection for only about three months. These findings point up the need for developing a more satisfactory immunizing agent--an antibacterial vaccine with a longer effective life, a long-acting toxoid or a combination of both. Several research teams have reported success with preparation of potent toxins for use in attempting the development of such a toxoid. Toxins will cause a cholera-like, fatal illness and, in preliminary studies, this action seems to be prevented by antitoxins created by injection of toxoids. Grantees at Johns Hopkins University last year reported the encouraging development of a canine model for cholera study which will facilitate studies on methods for treatment and prevention.

Tuberculosis

Tuberculosis remains a major health problem in the United States, where it takes 10,000 lives and accounts for 50,000 new active cases annually.

Scientists at NIAID's Rocky Mountain Laboratory and a grantee at the University of Montana continued their efforts to develop an experimental vaccine made from components of the bacterial cell wall. They reported in 1967, for example, that intravenous inoculation with a single dose of BCG cell walls treated with light mineral oil induces significant resistance in mice against aerosol infection by Mycobacterium tuberculosis for at least seven months. This resistance was longer than that conferred by living BCG vaccine. University of Wisconsin grantees also reported progress in devising ways of storing suspensions of mycobacteria at low temperatures for animal studies.

Role of Bacteria in Chronic Respiratory Diseases

Studies on the role of bacteria as possible contributors to the development of emphysema and other chronic respiratory diseases are being conducted by a number of grantees. An encouraging contribution has been a report from the University of Utah team on the diagnostic usefulness of transtracheal aspiration, a method of withdrawing secretions from deep in the lung.

The initial encounter between host and infectious agent is a critical factor in pulmonary bacterial disease. Clinical infection may be averted if the bacteria are killed promptly by the defense mechanisms or are removed mechanically. Work with mice by Harvard University grantees illustrates one result of damaging the lung's defenses. Removal of the mouse kidneys to cause acute renal failure damaged the intrapulmonary defense mechanisms. Pasteurella pneumotropica, bacteria which are

rapidly killed in the lungs of normal mice, multiplied easily in the lungs of the nephrectomized mice. Evidence also indicates that the role of cigarette smoke in the development of pulmonary disease may be its impairment of the integrated defensive function at the respiratory membrane level of the lung.

In a study at the University of Southern California, scientists found that an irreversible alteration in lung structure (similar to that seen in emphysema) can be created by exposing mice for several weeks to air containing different concentrations of nitrogen dioxide ($NO_2$). The animals' alveoli were enlarged, some had ruptured walls, and their lungs were more susceptible to airborne bacterial infections. Other marked chemical inflammatory changes also occurred, but these subsided when the animals were removed from the nitrogen dioxide atmosphere. Studies are continuing to determine what alterations in the lungs may be brought about by both $NO_2$ and various infections.

L Forms

Increasing numbers of reports have indicated the clinical isolation of L-forms associated with human disease, as well as their lengthy survival in experimental animals and tissue cultures. L-forms are often produced during antibiotic treatment, but their significance in the maintenance and spread of disease remains unclear. Some findings suggest that their survival in the body and later reversion to the parent bacterial forms (with a cell wall) may lead to chronic bacterial infections.

Bacterial Toxins

Bacillus anthracis is the only aerobic (oxygen-requiring) spore-forming bacterial species able to cause epidemic infectious disease in man and other mammals. In recent years, experimental evidence from a number of grantees has suggested that anthrax toxin contributes significantly to the development of the infection and that the central nervous system may be the toxin's primary target. Understanding the processes that lead to damage in anthrax may lead to better understanding of other diseases in which a toxin or some other extracellular product is involved in producing disease.

A New York University grantee, for example, is working with Bacillus cereus, a species closely related to B. anthracis. Although it is not a notable pathogen in mammals, the destructive cell changes (cytopathology) resulting from the biological activities of B. cereus in tissue culture is comparable to that of the toxin synthesized by Clostridium perfringens (the cause of gas gangrene in humans). The B. cereus toxins produce localized tissue destruction, but generalized infections or toxic deaths in animals are rare. In contrast, the highly

toxic action of C. perfringens infection causes death in experimental animals. This paradox of similar biological activity but greatly differing effects on the host tissue is being investigated in the hope of uncovering the subtle differences which may give insight into the fundamental mechanisms of virulence.

In other research on bacterial toxins, grantees at Vanderbilt University have found evidence that botulinus toxin (which produces botulism, a type of food poisoning) exerts a direct effect on the heart. They detected type B toxin in the serum of patients who had eaten toxin-contaminated food and suggest that inoculating mice with serum from patients suspected of having clinical botulism may prove a useful test for confirming the diagnosis.

## MYCOPLASMAL DISEASES

The organisms known as mycoplasma--which are usually smaller than bacteria but structurally so similar to the bacterial L-forms that differentiation is difficult--present many puzzling features. A number of mycoplasma are true animal pathogens, and one of the eight accepted human species, Mycoplasma pneumoniae, is a major cause of primary atypical pneumonia in man.

In work with this species, NIAID scientists reported that patients treated with tetracycline and erythromycin showed rapid clinical improvement but continued to excrete M. pneumoniae after therapy. Persistence of the organism could not be explained by insufficient levels of the drugs in respiratory secretions or by the emergence of antibiotic-resistant organisms. Carriers of the organism, particularly if they retain the persistent cough which so often follows M. pneumoniae pneumonia, may be important in the spread of this infection.

Efforts continue to improve the moderate degree of protection provided by an experimental M. pneumoniae vaccine. Chemical studies of an M. Pneumoniae hapten (a chemical fraction that determines its immunological specificity) may lead to an active immunizing preparation.

Intramural scientists also seek the significance of the recent isolation of M. hominis from a few fetuses aborted during the first trimester of pregnancy, while other Institute studies concentrate on the role of mycoplasmas in animal tumors.

## FUNGAL DISEASES

The increasing reporting of systemic fungal diseases and the inadequacies of diagnostic methods and therapy are important considerations in the Institute's clinical and laboratory research programs in mycology.

Clinical study of patients with cryptococcosis and efforts to purify antigens for use as diagnostic and epidemiologic tools are under way. One convenient presumptive diagnostic test has been developed by Institute scientists, based on the finding of low levels of cerebrospinal fluid sugar in patients with cryptococcal meningitis.

Some light has been cast on the development of cryptococcosis by grantees at the University of Oklahoma. They found that the capsule surrounding Cryptococcus neoformans is apparently a factor in the virulence of the fungus, possibly inhibiting its destruction by human white blood cells.

Institute investigation of 75 synthetic compounds last year showed 18 had some antifungal activity for C. neoformans and Histoplasma capsulatum, the latter being the cause of the systemic disease histoplasmosis.

In addition to earlier studies linking bats more firmly to human cases of histoplasmosis, grantees at Tulane University last year found that free-tailed bats are susceptible to experimental infection with Blastomyces dermatitidis, the yeastlike fungus that causes North American blastomycosis. The possibility that in nature bats may serve as vectors for the dissemination of other disease-causing fungi by excreting contaminated feces is receiving increased attention.

Work with mice by a grantee at the University of Chicago disclosed a toxic enzyme which may be responsible for the tissue damage in a human fungal disease prevalent in tropical countries and occasionally found in the southern United States. The fungus, Streptomyces maduras, causes maduramycosis or "Maudra foot", a disease which is so difficult to treat that amputation of the infected leg is often required.

## PARASITIC DISEASES

Toxoplasmosis is perhaps the most important parasitic disease in the United States. It is being increasingly recognized as a cause of eye disease, as a serious complication in patients undergoing cancer chemotherapy, and as a cause of abortion or infant death.

Worldwide, malaria and schistosomiasis outstrip all other parasitic infections in importance as causes of illness or death. Although both are most prevalent among indigenous populations in the tropics, both diseases sometimes threaten Americans: malaria principally as a military disease in southeast Asia; schistosomiasis as a diagnostic and therapeutic problem in Puerto Rican and Filipino populations in the cities.

Toxoplasmosis

A fast, simple technique for the diagnosis in newborns of congenital toxoplasmosis--a parasitic disease which is often fatal--has been developed by grantees at Palo Alto Medical Research Foundation and Stanford University. There has been need for an effective tool for diagnosing the acute stage of this disease, particularly in newborn infants, because only if therapy is started early is there hope of preventing extensive tissue destruction by the parasite and possible crippling effects such as mental retardation and blindness. The technique identifies certain antibodies, which do not normally traverse the placenta, formed in response to infection in the unborn child.

Institute studies using the electron microscope have provided information on Toxoplasma division which is being used for investigation of the effects of various drugs known to inhibit the parasite. For example, study of pyrimethamine-treated tissue cultures of infected monkey kidney cells has shown a disruption of the parasites' normal division process.

Other Institute studies have shown that more than 90 percent of leukemia patients studied have anti-Toxoplasma antibodies at autopsy. Development of these antibodies appears to take place about the time the patients begin receiving large-scale blood transfusions. Detailed studies of selected patients with leukemia who have no such antibodies are under way to learn whether they result from the transfusions or from activation of latent infections.

Malaria

Malaria eradication efforts have met with multiple problems, and significant increases in incidence have been reported from a number of areas. The emergence of parasite strains resistant to antimalarial drugs poses a serious threat.

A simple technique has been developed by grantees at the University of Georgia for preserving strains of malaria parasites for an indefinite period. This may make feasible the establishment of "banks" of malaria strains. Working with chicken malaria, the scientists found that parasites within the salivary glands of mosquitoes remained viable and infective for more than two years when frozen in liquid nitrogen at -197 degrees Centigrade. Preservation of malaria strains in this manner should make it possible to work with "parent strains" for indefinite periods of time, avoiding a problem involved in long-term studies on drugs: results at different periods of experiments sometimes are not comparable because routine transfer of the parasites from host to host at short intervals may result in alteration of the biological characteristics of the strain.

NIAID scientists have evaluated alternative methods for treatment of chloroquine-resistant falciparum malarias (the most severe forms of human malaria). Studies last year included the repository drugs CI-501 (cycloguanil pamoate) and CI-564 (CI-501 plus diacetylaminodiphenyl sulfone or DADDS). CI-501 was found to have no demonstrable effect against three resistant strains of Plasmodium falciparum. CI-564 was shown to provide only short-term protection against infection and apparently cannot be relied on for treatment of the resistant falciparum malarias.

The increase in the occurrence of relapses with vivax malarias from Southeast Asia has also caused apprehension. In the wake of evidence that at least some strains of P. vivax are producing relapses in the face of "curative" therapy with primaquine and may be resistant, the effectiveness of normally-used doses of primaquine is being assessed against these strains in volunteers.

Institute studies on the selection and persistence of drug-resistance in the rodent malarias revealed that resistance to primaquine is more slowly acquired than resistance to chloroquine, pyrimethamine, or quinine. Stability of resistance, once acquired, was shown by chloroquine- and quinine-resistant strains.

Schistosomiasis

Observations by grantees at Johns Hopkins University have recently provided leads for further studies which could result in better treatment of schistosomiasis. Studies with the drug called TAC have revealed the biochemical mechanism of its action on the adhesive organs of the worms, and have yielded additional knowledge about cessation of egg production by worms affected by the drug.

A grantee team at the Federal University of Minas Gerais, Brazil, found a derivative of Miracil D, Hycanthone, to be more effective than the parent drug against schistosome infections in rodents and monkeys. It is now being tested in patients.

An important question in epidemiological studies of schistosomiasis has been whether the number of eggs appearing in the urine or feces of patients can be used to estimate the number of worms in the infection. In studies on mice infected with Schistosoma mansoni, workers at the University of Chicago showed that egg production remained constant as the worms became older but the number of eggs excreted by the mice decreased. They suggest that antibody may inhibit certain enzymes produced by the eggs which are necessary for their penetration of body tissues and hence their elimination in body waste.

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Studies of human patients by Institute scientists at the Hospital Edgar Santos in Bahia, Brazil, sought the relation between the amount of infection with S. mansoni and the lesions and disease produced. Evidence indicated that the number of eggs in the feces is a measure of the intensity of infection and lends support to the theory that worm death causes the decrease in egg excretion in older infections. Autopsy studies demonstrated the importance of heavy infection in man for the production of disease. A unique contribution was the autopsy finding that no intestinal disease of clinical significance could be associated with infection.

Amebiasis

Amebic dysentery, with the liver complications which frequently accompany it, continues to be an important disease in tropical areas and, to a lesser extent, in many temperate regions of the world. Relatively few drugs are of proved efficacy. The oldest and most widely used, emetine hydrochloride, is well known to affect the heart muscle (myocardium). A synthetic preparation, dehydroemetine, was introduced recently with claims for reduced toxicity. Two new drugs, Ambilhar and metronidazole, have been shown to be potent intestinal and systemic amebicides, but their toxicity for the heart has not been known. A grantee at the South African Amoebiasis Research Unit compared the toxic effects of these four drugs. The investigation showed that, on the basis of electrocardiographic findings, great caution should be used in treating patients with either of the emetine compounds or with Ambilhar because of potential myocardial damage, while metronidazole promises to be a uniquely safe and effective amebicide, especially for patients with heart disease.

One of the major obstacles in amebiasis research has been the difficulty of differentiating between pathogenic and non-pathogenic strains of Entamoeba histolytica, the causative organism. Recently, however, grantees at the Louisiana State University and Instituto Maranon in Madrid, Spain, developed a culture medium in which only the pathogenic strains produce characteristic enzyme activity. This biochemical method should augment earlier techniques used for identification.

Filariasis

Filariasis is another widespread human disease which, like schistosomiasis, is caused by parasitic worms. Control of filariasis by using drugs--to reduce the number of worms and thus interrupt transmission--has had varying success because of a few remaining residual infections. Grantees at the University of California, Los Angeles, have recently

shown that for optimal results the dosage of the drug diethylcarbamazine must be somewhat proportional to the level of microfilarial (larval) parasites in the blood.

It had been generally accepted that the number of larval parasites per unit of blood at peak infection is roughly related to the total larval population in the host. This concept was disproved by Institute scientists in exchange transfusion studies performed in dogs. Despite removal of more larvae than were initially estimated to be present, the number of microfilariae counted before, during, and after the exchange transfusions remained essentially unchanged. These studies show that different mechanisms control the total of larvae in the host and regulate the number present in peripheral circulation.

Vectors of Parasitic Diseases

Work at the University of Notre Dame presents an interesting example of the way in which research projects may evolve into unexpected avenues of great promise. In a productive study on the genetics of mosquitoes, a grantee team has recently discovered that female mosquitoes are inseminated only once and that subsequent insemination is inhibited by a substance from the accessory gland of the first male. The reaction occurs in at least 12 species of mosquitoes, including two of importance in the transmission of malaria and filariasis. When females were injected with an extract of male glands, mating occurred but sperm were not stored. Essentially, the female mosquitoes were sterilized. The investigators are now seeking practical ways of using this substance. The ideal procedure would be to feed it to the aquatic larvae and have adult females emerge already sterilized. This would provide a potent mosquito control weapon as an alternative to the use of insecticides, which pose such problems as residual toxicity to other forms of plant and animal life.

In another project dealing with mosquitoes and their role in human disease, grantees at the University of Illinois have studied hypersensitivity to mosquito bites in persons known to have prolonged previous exposure. One important observation was that both delayed and immediate hypersensitivity responses disappear in those exposed repeatedly.

At Ohio Agricultural Research and Development Center a grantee scientist has found that mites which are vectors of human disease vary in the efficiency of transmission in accordance with atmospheric humidity. His study has shown that the optimum humidity for mites is 90% and that in drier atmospheres they must obtain frequent blood meals to survive. Information of this type has importance not only in understanding the role of these arthropods in transmitting disease but perhaps also in formulating effective control measures based upon the biological requirements of the vectors.

Research in other Parasitic Diseases

The development of an effective non-allergenic vaccine against Chagas disease--which is estimated to affect 7 million people in South America--has been delayed and immunochemical studies hampered by the complexity of the medium for the cultivation of Trypanosoma cruzi, which causes the disease. Last year a grantee at the University of Montana reported development of a protein-free medium which apparently promotes growth over a long period and produces large quantities of the parasite which may easily be harvested. The medium may offer advantages, particularly in the production and testing of antigens for T. cruzi vaccine.

Leishmaniasis

Visceral leishmaniasis, or kala azar, a relatively common human parasitic disease in the Mediterranean area, northern Africa and the Orient, usually is fatal if untreated. Early diagnosis thus is important but has been hampered by the insensitivity of conventional test procedures. Using immunoelectroadsorption--a new and sensitive method for detecting antibodies--grantees at the Rockefeller University have been able to detect antibodies in experimental hamsters within one week of infection. If the results obtained in animals can be reproduced with leishmaniasis in man, this new procedure could be a rapid, specific and simple method for the early diagnosis of the disease.

# HIGHLIGHTS OF RESEARCH PROGRESS

during 1967

from

## NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Research programs of the National Institute of General Medical Sciences are characterized by the continuous flow of knowledge from a variety of small fundamental research projects into larger research centers specially structured to apply new knowledge to the solution of major health problems.

Work on a sustained basis by many qualified investigators is vital, for example, to develop core multidisciplinary research activities aimed directly at the achievement of specific health goals. Such goals for the Institute include understanding of the genetic basis of human diseases, the production of safer and more effective drugs, and the improvement of diagnostic and therapeutic measures in medicine.

In line with these objectives and emanating from a mixture of fundamental and applied research, some recent accomplishments by Institute-supported scientists are summarized in the following highlights of research.

Just as the 20th Century is known as the atomic age, the 21st, many scientists believe, may be known as the age of DNA. Once man can purposefully manipulate this master chemical--whose full name is deoxyribonucleic acid and whose function controls the heredity of all living organisms--he may find not only a cure for major illnesses but also a means to make himself stronger, healthier, and more intelligent.

In 1967, the door was opened at least partially to such possibilities when a Nobel laureate supported by the Institute and his co-workers succeeded for the first time in manufacturing a synthetic DNA which displays the full biological activity of the natural molecule in living organisms. This scientist, Dr. Arthur Kornberg of Stanford University, and his associates successfully synthesized the fully infectious DNA of a virus, representing five to six genes. The test tube product, when taken up by its bacterial host, orders the production of exact replicas of itself and synthesizes all components of the infectious virus. In effect, it represents an important step forward in learning how viruses duplicate in cells and how DNA polymerase or similar enzymes act to make new DNA. It may, in time, have significant health applications, as in the understanding of certain forms of cancer and their prevention or therapy.

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If, for example, the complex DNA of a particular virus can be duplicated in a test tube with exactness, it should be possible to copy other viruses. By the same token, it should be possible to modify their structure by putting in alternative or fraudulent building blocks to create new forms of viruses. These synthetic viruses could then be used to infect cells and their biological effects could be observed.

Such an approach conceivably can lead to greater understanding of the roles DNA-type viruses may play in cancer, and thus to an understanding of the basis of origin of certain cancer cells and perhaps to their control. For example, DNA found in polyoma virus produces a variety of cancers in many animals. It is reasonable to expect that with a synthetic system for producing variations in the structure of polyoma DNA, specific genes in the virus which direct the cancer response can be determined. Eventually, such viruses might be changed to produce a non-cancerous response.

A possibility in the more distant future--perhaps in the next century--might be the careful manipulation of laboratory synthesis of DNA as a means to modify defective or mutant genes in a directed way to benefit many aspects of human health and intelligence.

The achievement of Dr. Kornberg and his associates would not have been possible, of course, without the collaboration and assistance of many scientists, including several Institute grantees who worked independently and without precise knowledge of the others' work.

Dr. Robert L. Sinsheimer of the California Institute of Technology--who is doing extensive research with support from the Institute--performed much of the developmental work on a virus called Phi X 174, the one used in Dr. Kornberg's work. This virus was chosen because it had been studied extensively, because it is a comparatively small and simple virus, and because its inner core of DNA is single-stranded rather than double-stranded. The single strand characteristic made the DNA easier to use as a pattern for making duplicate copies.

Other Institute grantees at Stanford and at the Albert Einstein College of Medicine in New York played significant roles in the discovery of a joining enzyme that--in addition to the enzyme DNA polymerase which Dr. Kornberg purified--was essential to his recent success.

Widely diversified and continuing efforts that led to the Stanford discovery thus demonstrate how Institute-supported scientists are contributing by a variety of attacks to a richer understanding of life processes that may be applied to the betterment of man's health.

Another example of Institute-supported fundamental research having important potential for the clinical treatment of patients may be cited. Living systems--man

and animals alike--possess delicate biological rhythms that control basic activities such as rate of metabolism and daily variation in bodily activity. It is generally known, for instance, that body temperatures rise in the morning, some hormones fluctuate with regularity, and that death occurs more often at night, possibly as a result of such biological rhythms. At the University of Pennsylvania, scientists have identified one of these "biological clocks" for the first time at the biochemical level.

Dr. Britton Chance and his associates have pinpointed phosphofructokinase--one of the enzymes that breaks down glucose into various end products--as a regulator of rhythmical activity involving cellular metabolism of glucose. This discovery has important potential for physicians, who eventually may apply such knowledge in determining the times of day when drugs administered to patients would have maximum beneficial effect. These scientists also are exploring possible interactions between short-period oscillation of co-enzyme concentrations and changes in other biological systems that exhibit natural rhythms, such as the rhythmic beat of the heart. They believe interactions among several of these internal oscillations may determine 24-hour rhythms in the body. Continuing information about these phenomena may have value in controlling fatigue, regulating body temperature, and understanding many other vital physiological functions.

An enzyme is a protein that controls the rate of biochemical processes in the body. Through enzyme induction--a process whereby levels of enzymes are increased--drug metabolism in the liver may be accelerated and toxic agents converted more rapidly into harmless material. Among the leading investigators of enzyme induction in high animals are physicians and scientists working with Institute support at Emory University in Atlanta. They are among a select and highly-skilled group of biochemical pharmacologists with extensive experience in studying and analyzing the precise actions of drugs and chemicals in both animals and man.

In 1967, the Emory scientists expanded their research efforts to include a laboratory to explore the specific molecular characteristics of certain drugs and to associate these characteristics with the mode of action of drugs in the body. For example, they are using deuterium (heavy hydrogen) as a tracer element to study metabolism of fats and amino acids in the body. Such research is part of the current expansion of pharmacology and toxicology to include molecular or sub-microscopic investigation. By focusing more sharply at molecular levels, pharmacologists expect to determine the nature of the reaction between an individual molecule and some receptor site inside the body--a basic research activity with exciting implications in gaining better understanding of all drug mechanisms.

These and other scientists have shown the concentration of a drug in the blood--not the dosage prescribed by a physician--determines the therapeutic effect of the drug. Therefore, depending upon the rate of absorption and metabolism, one patient might require many times the dose of a drug in order to receive a therapeutic effect

equivalent to that of another patient on the same drug. At the Karolinska Institute in Stockholm, scientists found a 36-fold difference in the amount of a drug that reached the blood of a number of test patients even though the same dose of the same drug (a well-known antidepressant) was administered to each individual studied. These scientists are further investigating the same drug to determine possible relationships between the amount of drug in the blood and drug side effects as well as antidepressant effects. Meanwhile, studies by the Clinical Pharmacology Section at Emory University have revealed that an effective dose for individual patients on guanethidine, a potent drug to lower the blood pressure, varies from 5 milligrams to 400 milligrams, a dramatic 80-fold difference.

At the University of Iowa, scientists at the Institute-supported Oakdale Center for Research in Biochemical Pharmacology and Toxicology are engaged vigorously in research concerning the detection of toxic effects of many chemicals to which man is exposed therapeutically, environmentally, occupationally, and accidentally. For example, their research is focusing on how certain drugs and chemicals may produce malformations in the fetuses of animals. The thalidomide tragedy has provided great social incentive for such fundamental research. This work also is directed toward determining what time periods during pregnancy may be the most dangerous to administer a given drug and why some agents are more hazardous than others at particular stages of pregnancy. During the past year, the Iowa group has developed a number of improved animal tests for detecting pharmacological agents harmful to the fetus.

In clinical pharmacology studies supported by the Institute at Tufts University, scientists are monitoring patients in several Boston hospitals to determine how an administered drug is therapeutically effective, how often it fails to produce desired effects, and how frequently it precipitates adverse reactions. In an 18-month study at Lemuel Shattuck Hospital and Boston City Hospital, these investigators monitored 13,868 consecutive uses of drugs among approximately 1,400 patients. Results carefully tabulated by computer showed 900 instances of alleged adverse drug reaction and involved approximately 6 percent of all drugs administered. It was possible to evaluate thoroughly over 80 percent of these instances, of which adverse reaction in 50 percent of the cases was severe enough to cause discontinuance of the drug in use. Most significant is that of a total 300 hospital deaths during the time of the study, eight were attributed to drug reactions. In another 26 cases, the investigators believe drugs were a major contributing factor although not directly the cause of death. The importance of such information in safe and effective use of drugs cannot be overestimated.

Important relationships were discovered also between drug use and various genetic factors, such as sex and blood type, as well as variances in drug effects with age. For example, heparin, an anticoagulant, was found to produce serious bleeding much more often in older female patients (80 percent of the time) than in males or younger females (almost zero). Similar evidence suggests that barbiturates also behave

quite differently in patients with different blood groups. Laboratory studies are now being established to pursue the biochemical nature of these variances. Meanwhile, the systematic collection and evaluation of data in the Tufts' study has been developed to the point where it is now possible to spot very quickly, within several cases, any trend of serious adverse reaction ensuing from the use of any given drug. Because all the data are controlled by computer, retrospective studies also can be done very rapidly to determine whether other drugs might be involved. Just recently a third hospital, Peter Bent Brigham, joined in the Boston study. Although few if any comparable epidemiological drug studies have been undertaken, this kind of research is extremely important to clinical medicine in that it will lead eventually to the development of predictive techniques to protect susceptible patients from severe illness and possibly fatal adverse reactions.

In the area of drug research technology, Institute supported scientists, notably Drs. Bo Holmstedt and Folke Sjoqvist at the Karolinska Institute and Dr. Keith Palmer at the Research Triangle Institute in North Carolina, are in the forefront in developing and using some of our most powerful tools to investigate drug toxicity in man. The Swedish scientists have pioneered the use of gas chromatography and mass spectrography linked sequentially to a computer to separate and identify drug metabolites systematically and rapidly in human blood plasma. Indications are this system is at least three times more sensitive than conventional electron capture methods, and as many as 200 separate blood analyses may be done in a single day. Dr. Palmer is using similar techniques to identify drug metabolites in human plasma and to produce these particles in highly purified form in order to evaluate further their therapeutic effectiveness and toxic qualities.

Biomedical engineering--the application of engineering principles in biology and medicine--continues to be emphasized strongly in the Institute's research programs. Of particular interest are both fundamental and collaborative studies underlying the development of new and improved methods for the diagnosis of disease, administration of anesthesia, intensive care for critically injured patients, the development of hospital information systems, and the automation of clinical pathological laboratories.

Research in the automation of clinical laboratories applies not only to improving the speed, accuracy, and quality of diagnostic tests but to many important investigations relating directly to the delivery of better medical care. Within the context of this research goal at a very fundamental level, Dr. Jesse W. Beams of the University of Virginia, working with Institute support, has developed a new ultracentrifuge that permits highly specific and precise determinations of the molecular weight and volume of protein materials, including viruses and body substances. These measurements are important to assessing the biological activity of such macromolecules. Dr. Beams' machine employs a magnetically suspended rotor that moves freely and without distortion in a vacuum under constant temperature and at speeds that may be varied from 1 to 10,000 revolutions per second. Further refinements include sensors

which record automatically vital data concerning the temperature, pressure, density and electromotive forces produced in the ultracentrifuge cell. This technology recently was a basic factor in the development by other scientists of new and better vaccines from highly purified virus fractions separated on the basis of both molecular weight and sedimentation properties. For his ultracentrifuge development work, Dr. Beams was awarded one of the National Medals of Science for 1967, the Government's highest honor for distinguished achievement in science.

At a more applied level of research, Dr. Norman Anderson of Oak Ridge National Laboratory and other scientists supported by the Institute are developing a high resolution analytical system that already has identified 130 regularly appearing components in urine. The significance of this research is better understood when it is realized that only 30 such components can be identified by methods currently in general use. Studies now are underway to relate these components in urine, blood, and other body fluids to a patient's health and to altered metabolic processes relating to disease.

At the Medical College of Virginia, Dr. Ian Bush is working with Institute support to develop a completely automated system for analyzing steroids in urine by paper chromatography. The new analytical system, integrated with a computer, controls the functions of the machinery while acting simultaneously as a data processing system. This work may have important application in the detection of certain forms of cancer in women through the high resolution analysis of steroid patterns in both urine and blood which are altered by the disease. Automated procedures to analyze biological fluids also can be useful in detecting abnormal endocrine levels often associated with adrenal disorders such as Addison's disease and Cushing's syndrome. Other systems of automated urinalysis--along with serum tests--may be equally important in facilitating the early diagnosis and treatment of diseases such as phenylketonuria (PKU), a congenital metabolic disorder often associated with mental retardation.

The Institute is examining numerous techniques for monitoring physiological functions periodically throughout a person's life, thus helping to predict the onset of disease when deviations from normal patterns are observed. Such procedures conceivably can provide individual profiles on each patient under a doctor's surveillance. Of special significance are subtle changes in chemical components of blood that often precede illness and often are overlooked in current laboratory testing procedures. Scientists at Marquette University, for example, have developed a speedier, more accurate laboratory test for detecting Vitamin $B_{12}$ deficiency, the major factor in pernicious anemia, and a chemist at the Milwaukee Blood Center has invented an inexpensive method for producing ion-selective membranes which will facilitate certain diagnostic procedures.

Another research group at the University of Wisconsin has developed and is applying a new method for separating and identifying isoenzymes to an automated system for the clinical diagnosis of heart attack.

With support from the Institute, scientists at the University of California in Berkeley and at the University's San Francisco Medical Center are developing computer-controlled instruments and data collection systems for clinical chemistry and hematology and for the most advanced automated diagnostic procedures known in bacteriology. The Berkeley scientists have automated procedures that now identify more than 50 disease-producing microorganisms. Among other things the continuing development of this program is expected to result in more effective evaluation of antibiotics to combat infectious diseases.

At Stanford University considerable advances are being made with Institute support in the development of laser microprobe technology for histo- and cytochemical analysis. By this technique, ultramicro concentrations of zinc, magnesium, and other trace elements may be measured within a single cell. This research is part of the continuing effort to develop more accurate quantitative analysis of such elements in cells and tissues. The technique begins with vaporization of a tissue sample by a laser beam passed through a microscope. Spectral lines of elements in the rising vapor are photographed and evaluated quantitatively by optical scanning and recording techniques. It is expected such new analytical methods will provide important information on the relationship of various metallic trace elements to disease, such as the relationship of zinc to cirrhosis and cancer, cadmium to kidney disease, selenium to muscle metabolism, and aluminum to diseases of the lung--all related to the general problem of toxicity of common metals.

Engineers working at Northwestern University with Institute support have developed an ultrasound color phase-imaging system that produces bright, instantaneous images of pulsating blood vessels, muscles, and other tissues not normally visible in conventional X-rays. The colors in the new system represent varying rates of acoustical impedance encountered as the sound waves pass through a hand, foot or other portion of the body in a water medium. Preliminary studies indicate the new instrument is 20 to 40 times more sensitive to changes in body tissues than a black and white ultrasound imaging system developed earlier by these investigators which has shown important potential application in clinical diagnosis. Unlike some X-ray methods, the ultrasound system does not require the use of contrast media. As an important adjunct to X-ray, this system can provide the physician with a new, distinct, and in some cases safer set of eyes for the diagnosis of disease and injury.

Slight and subtle elevations in skin surface temperature have been linked to certain increased cellular or metabolic activity sometimes indicative of cancer, infection, or other disorders. These changes have proven too difficult for the physician to interpret by routine physical examination or standard diagnostic procedures. At Temple University, radiological scientists supported by the Institute are employing sensitive scanning radiometers to produce two-dimensional heat pictures, or thermograms, of the skin's thermal patterns. This process--known as medical thermograph--is a new and increasingly important diagnostic tool for evaluating physiological or pathological changes that deviate from normal patterns and in time may prove to be a valuable indicator of disease.

In addition to clinical studies, the Temple scientists are conducting basic research on physiological mechanisms leading to the production of thermographic images. Heat sources are implanted in laboratory animals and the roles of conduction, blood flow, and tissue patterns are analyzed carefully and correlated with observed thermographic patterns for the development of more sophisticated diagnostic procedures.

The maintenance of adequate pulmonary ventilation is absolutely essential for oxygen intake and carbon dioxide elimination in all individuals. Scientists in the Institute-supported Biomedical Engineering Research Program at Johns Hopkins University have developed a new instrument to monitor continuously tissue carbon dioxide levels through the intact skin and thus indicate to the physician whether proper lung function is being maintained in eliminating carbon dioxide from the body. Using a diffusion system that employs special electrodes, the Maryland team detected the most subtle changes in the levels of carbon dioxide through the skin of human patients. Adapted to clinical use, this instrument could, for example, be particularly valuable in detecting delicate respiratory problems in newborn infants.

At Case Western Reserve University, Institute-supported engineers and scientists are perfecting small devices to monitor body temperature, respiration rate, pulse rate, and muscle spasms. One such instrument package, mounted on a paraplegic patient at Highland View Hospital in Cleveland, provided continuous biomedical data on the patient for a period of several weeks. These scientists also have reported favorable results in laboratory evaluation of implanted electronic systems remotely to control electronic stimulation of heart, bladder, nerve and limb tissues. Such implantable systems potentially are useful in helping to rehabilitate the physically-handicapped and in restoring activities of muscles and nerves of the body which have been impaired.

At the University of Maryland, scientists supported by the Institute have produced electric power from a living animal, enough energy their preliminary experiments have shown, to power continuously a heart pacemaker in a human patient. At present, pacemakers are powered by a series of small batteries. There also is considerable interest in electric energy as produced in the body as a means of driving a completely implanted heart. The Maryland group achieved its results by placing an electrode in the bloodstream of the heart and another outside the heart of a laboratory animal. A sustained power level two to four times that needed to power a pacemaker was achieved. The Maryland investigators are conducting further research to determine the long-term reliability of such energy sources.

Investigating the functions of cells and tissues is a major unifying thread of research in the biological sciences. Practically all biological phenomena are being studied at the cellular and subcellular levels. The trend toward studies of the fine structure of cells and the identification of subcellular particles and their relationship to disease is on the increase and is being encouraged.

Hereditary factors play key roles in many diseases affecting man, including gout, diabetes, and numerous familial diseases. In addition, extensive studies of chromosomal deviations have pointed to the possible relationship between these deviations and cancer. Definite cause-and-effect relationships between gene action and specific genetic diseases such as galactosemia, phenylketonuria (PKU), sickle cell anemia, Down's syndrome, and cystic fibrosis have been determined. Because of the important role of both human genetics and genetic chemistry in the continuing and crucial combat against hereditary anomalies, the Institute supports many projects in these interlinking research areas.

An inherited disease fundamentally is a molecular disease. A change in structure of the basic genetic molecule results in a change of the structure of the formed protein. Such changes may be lethal to the cell but if perpetuated in the organism they almost always are harmful. Study of the biochemical nature of genetic materials and the consequences of their alteration is known as genetic chemistry. By the same token, mutations (spontaneous or induced changes in genetic material) are known to occur in the hereditary process and therefore are intimately related to genetic chemistry.

Genes are located on chromosomes within the nucleus of a cell. Chromosomes may be described as double strands of DNA composed of many different sequences of four nucleotides or building blocks. In the joining of the two DNA strands, a normal pattern of "pairing" between the different nucleotides occurs. Errors in base pairing may produce a mutant gene and can be introduced by chemical mutagens which either mimic the natural nucleotide or chemically alter them. Once such chemical error has been introduced, it may be faithfully copied, be transmitted to the individual's progeny, and thus be expressed by the body's production of altered proteins which may be impaired in function.

It had been assumed until recently that during DNA replication and the formation of a new cell, new nucleotides tended to align themselves along the old parent strands. They would then be joined to form a new strand, their linking together facilitated by the enzyme DNA polymerase. The enzyme was not considered to be directive, in the sense that it "selected" the proper nucleotide for the linking, which is known as polymerization.

However, Dr. Joseph Speyer, an Institute-supported scientist doing research at Cold Spring Harbor Laboratory in New York and later at the University of Connecticut, has found that the joining enzyme actually does play a role in base selection, and that a mutant DNA polymerase will cause mutant DNA. Conceivably, this enzyme could be a source of spontaneous mutations in higher animals that could lead to genetic defects. This work also has demonstrated a previously unrecognized feed-back from proteins to nucleic acids, since the new concept could explain why some substances that cause errors in protein synthesis can be mutagenic.

In recent years, insufficient supply of pure molecular materials has hindered the research efforts of geneticists and molecular biologists. To solve this problem the Institute initiated a collaborative research project with Oak Ridge National Laboratory scientists to develop new and economical methods for separating and producing nucleic acid molecules in meaningful quantities for research purposes. As a side product of their developmental work, these investigators have been able to separate and purify relatively large amounts of transfer ribonucleic acid (tRNA), one of our most important genetic materials. The Institute thus has been able to supply highly-purified tRNA to some 25 eminent research scientists. Continuing studies by these investigators should help to enhance considerably knowledge of the role played by this molecule in the synthesis of proteins in the cell.

At Duke University, the University of Wisconsin, and Stanford University, physicians and scientists supported by the Institute have contributed importantly to the typing of human tissue antigens. Each has produced key evidence supporting the existence and functional nature in man of a major chromosomal location--the Hu-1 locus--which appears to influence the acceptance or rejection of donor tissue by a recipient patient. Theoretically, this site, which may contain up to 25 genes, acts quantitatively to sense or recognize tissue that is foreign to the recipient body and, presumably, through the production of antibodies stimulates the activity of leukocytes or other mechanisms to attack and destroy donor tissues.

Dr. Bernard Amos, leader of the Duke group, by comparing the reactivity of white blood cells between siblings and the subsequent success or failure of skin and kidney grafts among these individuals, has found that the number and strength of antigens associated with the Hu-1 locus show a striking correlation to the survival and failure of grafts and transplants.

Skin graft studies by Dr. Fritz Bach at Wisconsin have produced findings quite similar to those of Dr. Amos, as has the work of Dr. Walter F. Bodmer at Stanford University. Both Dr. Bach and Dr. Bodmer are working also to improve upon white blood cell testing and possibly to elucidate further the role of the genetic Hu-1 factor.

In the short view, such knowledge could help extend the selection of tissue and organ donors to the general population and not be largely limited, as it presently is, to immediate or "blood" relatives of a recipient. In this respect, Dr. Amos recently observed that transplant operations using kidneys taken from cadavers have in a number of cases proved more successful than those utilizing kidneys living unrelated or remotely-related donors. Reasons for this are unknown but are being investigated. Dr. Bach and other geneticists meanwhile have postulated that within a few years persons may be typed according to their transplantation antigens as they are currently typed with respect to their blood groups.

These Institute-supported scientists also foresee that increased knowledge of immunogenetics could lead to vastly improved methods for specifically suppressing

the transplantation immune response. They theorize, moreover, that in addition to suppressing the immune response, its stimulation could lead to recognition earlier of foreign substances in cells. Such work represents further progress in the development of the genetics of tissue compatibility and incompatibility in man, a bold new direction for genetics research.

The Institute's support of fundamental biomedical science undergirds all of clinical medicine. However, the Institute also supports research in the clinical sciences per se, which may contribute greatly to the general health of the population. In medicine the programs, for example, are concerned with the clinical application of basic biochemical and biophysical investigations. Emphasis, however, is on anesthesiology, surgery, the therapy and management of trauma, and diagnostic radiology.

The nature of reaction to injury, shock, and tissue repair must be investigated at the basic research level in order to provide useful information for special Institute programs in the management and therapy of trauma. These fundamental studies are vital to understanding many things about the body's reactions to burns, penetrating wounds, and other forms of injury. For example, a key problem in treating trauma patients is tissue anoxia, a condition in which oxygen supply to body tissues is dangerously short of necessary levels. This reduction in oxygen supply leads quickly to irreversible cell damage.

To determine the crucial point beyond which anoxia cannot be extended without causing irreversible damage and death is one major objective of an Institute-supported trauma research center at the University of Pennsylvania. There, patients suffering from burns, hemorrhage, septic shock, and other traumatic conditions are treated and observed. Clinical studies are coordinated carefully with research in adjoining laboratories which makes use of animals, cells, tissues in culture, subcellular particles, and other basic materials.

At Tufts University, grantees are developing new methods to fight infection and speed the healing of burn injuries. Burn patients present a particularly challenging problem for scientists and physicians. Ten thousand people die of burns each year in this country while another two million are hospitalized for burns and their recovery may require many months. The research at Tufts is seeking to devise an effective combination treatment for burns, including topical application of anti-bacterial agents, the systemic use of antibiotics, and synthetic or prosthetic skin coverings to promote would healing. These scientists recently reported successful tests with animals of a new synthetic skin material consisting of an inner and outer layer of nylon velour with an impermeable center of silastic. They are now seeking to determine the optimum fabric design for this material and expect eventually to evaluate it as an adjunct to treating human burn patients.

Late in 1967, the Institute initiated support of a large new trauma research center at the University of Cincinnati. Among many aspects of trauma being

investigated in this center are clinical and basic investigations of the hazards of infection, benefits of treatment in an isolated sterile environment, effects on injured patients from ingestion of alcohol, differences in individual resistance and susceptibility to trauma, special problems associated with injuries of children and elderly persons, and psychological factors which lead to injury and influence patient recovery. At Albany Medical College in New York, another research team is using advanced computer systems to record and rapidly analyze physiological information on trauma patients as a means to speed and improve their treatment.

In summary, the Institute encourages the development and expansion of those basic biomedical and general clinical sciences which show the greatest promise for advancing knowledge of human health and disease. Through the selective support of a broad base of fundamental scientific investigations and interlinking clinical research efforts, the Institute is conducting a series of multidisciplinary research programs attacking diseases and public health problems of major national significance. Specific objectives of these programs are to improve health through safer and more effective use of therapeutic drugs; to open new pathways to the understanding and prevention and treatment of genetically-related diseases; to improve health services through the application of engineering knowledge to medical care; and to provide better diagnosis and therapy in general medicine.

In addition to reinforcing strongly the opportunities for achieving its own research goals, new knowledge gained through the Institute's fundamental research program contributes substantially to progress of the total overall National Institutes of Health research effort.

Highlights of Research Progress
during 1967
from the
National Institute of Child Health and Human Development

Population Dynamics

Despite a 25 percent decline in the United States birth rate since 1957, there is still no good evidence that today's average American family will ultimately be much smaller, according to an Institute-supported study at the University of Wisconsin and Princeton University.

Instead, the main explanation for the ten-year decline has been an increase in the average age of wives at childbearing, and an increasing tendency to space childbearing over a longer time period. In turn, most of the increase in childbearing age appears to be a consequence of later marriage ages.

The data on which the conclusions are based are part of a National Fertility Study which is compiling the reproductive and contraceptive histories of a national sample of 5,600 wives. Previous findings of the study, reported last year by Drs. Norman B. Ryder of Wisconsin and Charles F. Westoff of Princeton, indicate that 6.4 million women had used a contraceptive pill at one time and that another 4.7 million expected to use one in the future. Earlier findings also indicated that 21 percent of Roman Catholic wives under age 45 have used a birth control pill and that a majority of Catholic wives between 18 and 39 had not conformed to traditional Church doctrine on birth control.

In the present report of the study, the investigators presented figures showing the large extent to which the baby boom of the 1950's was caused by a trend toward progressively earlier marriage ages, and a consequent earlier age of the mother at childbearing.

Recently, however, a trend toward later childbearing, largely as a result of later marriages, has been responsible for lowering the birth rate. The lack of evidence for any parallel decline in expected family size is based on interviews with wives taken in 1965 and compared with interviews taken in two similar studies in 1955 and 1960.

The investigators nevertheless caution that predicting family size from the expectations of wives may be misleading. Delayed childbearing reduces exposure to the risk of accidental conception and increases the possibility of sterility through disease or accident. In addition,

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it gives couples the opportunity to scale down intentions concerning family size as a response to their exposure to alternatives to fertility, and it gives them experience with contraception which they may exploit to complete their family at the intended level. Further, the investigators predict unintended births will probably decline with the rise in education, the improvement of contraceptive methods, the diminution of religious resistance to effective means of fertility regulation, and the increase in government assistance to family planning programs.

The finding, however, that families continue to desire and expect relatively large families has important economic and social implications. Public acceptance of fertility control methods has been based on a belief in the right of couples to have as many children as they want, when they want them. If this freedom does not result in the expected decline in birth rate, it will be of the greatest interest to scientists and leaders responsible for coping with problems associated with rapid population growth.

Human Menstrual Cycles

A 30-year history of menstrual cycles covering more than 22,000 woman-years of experience clearly demonstrates that a regular 28-day cycle for most women is a myth. Not only is there great variation among women, but for each person there is a marked lack of regularity in menstrual interval in the early and again in the late years of reproductive life. Even during the relatively stable years, there is a gradual drop in interval of two to three days.

These menstrual interval studies were begun by Dr. Alan E. Treloar and associates at the University of Minnesota in 1934 and are being continued at the University and the National Institute of Child Health and Human Development. They provide the most authoritative information known to exist on changes in menstrual cycle from menarche to menopause.

The first few years of menstrual life, like the last few, are marked usually by a variation of short and long intervals. These transitional periods vary widely in length, but seem to occupy usually about five to seven years after menarche and six to eight years before menopause. There was no obvious criterion for judging the beginning of the menopausal period. The middle life, beginning about age 20, and occupying about two decades, is characterized on the average by linear change in both central tendency and variation. The general fall in interval through this age span is on the order of two to three days, depending on whether the median or mean is used for the typical value.

The study, comprising date for 22,754 calendar years of experience for all ages of reproductive life, showed the least difference between persons at about age 36. The characteristics of an individual menstrual

history sometimes altered with time and showed fluctuating divergences from an average pattern. Such information would seem to indicate that the practice of the rhythm method of birth control will present problems of uncertainty for all persons affected.

Vitamin Deficiency in Pregnancy

Evidence that folic acid deficiency in pregnancy is more common than previously recognized and that it causes damage to both mother and child has come from a group of New York Medical College investigators headed by Dr. Martin L. Stone.

Folic acid (part of the Vitamin B complex) and its derivatives are needed by the body to manufacture DNA, RNA, and protein. Deficiencies may therefore affect rapidly growing maternal, fetal, and trophoblastic tissues, resulting in abortions, early separation of the placenta, and possibly in congenital defects.

Non-pregnant women need 50 to 150 micrograms of folic acid in their diets each day. But, during pregnancy, metabolic changes and the demands of the growing fetus raise the daily requirement to between 200 and 800 micrograms.

When lack of the vitamin leads to megaloblastic anemia of pregnancy, it can readily be detected by reduction in red blood cells and platelet production in the bone marrow. How common it is in lesser forms which do not show up clinically has been the subject of some controversy.

Now the New York investigators have developed a rapid urine test, which they use in conjunction with other tests to determine more precisely the lack of folic acid. Their studies include normal non-pregnant and normal pregnant controls as well as selected patients with complications of pregnancy.

Among 250 unselected pregnant women tested, 55, or 22 percent, were deficient in the vitamin. Other studies report an incidence ranging from 7.9 to 18 percent. Folic acid deficiency in pregnancy is therefore calculated to be approximately 3 to 4 times as frequent as its extreme manifestation, megaloblastic anemia. The incidence was higher among twin pregnancies and in patients with toxemia of pregnancy and placental separation.

Heart Disease and Pregnancy

There has been a widespread clinical impression that pregnancy in a woman with cardiac disease depletes her reserves and shortens her life. There has also been concern and debate about the possible effect of pregnancy on the later course of rheumatic heart diseases. In some

cases, sterilization was suggested because it was thought that pregnancy would so greatly endanger the life of a woman with cardiac disease.

Dr. Leon Chesley, Research Foundation of the State University of New York, Albany, New York, has made a follow-up study of 134 women pregnant during the years 1931 through 1943, who had functionally severe rheumatic-cardiac disease. He has sought pertinent information that will have a direct bearing on current practices in management of cardiac pregnant cases. These women were followed up to 1966.

Analysis by life table, mean age at death, and mean length of survival has failed to show any effect of later pregnancies on the long-term prognosis of the cardiac disease of these women. The analysis was applied to the whole group and to various subgroups of women having heart disease of special severity. In the patients with rheumatic cardiac disease and surviving pregnancy, the pregnancy does not seem to have had any effect on the later course of the disease.

Initiation of Labor

Premature birth makes a significant contribution to infant mortality. However, we have an incomplete understanding of the process of childbirth. Such knowledge is crucial to preventing premature labor as well as to initiating the process in pregnancies that are overdue. It appears likely that the onset of labor is not due to a single cause, but to a number of factors which play some part in the specialized pattern of uterine contraction characteristic of labor.

One such important factor seems to be the development of the fetus. It has been recognized that human anencephalic fetuses (those having a partial or no brain) have been occasionally associated with abnormally prolonged gestation. In farm animals also, cranial and nervous system defects as well as defective or incomplete development of the pituitary gland have been associated with long gestation periods. This evidence suggests that the fetal pituitary gland plays an important part in the initiation of labor.

In recent studies by Drs. G. C. Liggins, P. C. Kennedy, and L. W. Holm at the University of California School of Veterinary Medicine at Davis, partial destruction of the pituitaries of otherwise normal fetal sheep resulted in either delayed onset of labor or failure of a pregnant ewe to come into labor spontaneously.

The results indicate that the mechanism by which the fetus influences maternal physiology depends on the integrity of the fetal pituitary and possibly to that part of the brain to which the pituitary is attached--the hypothalamus.

Human Growth Hormone in the Fetus

Research on the role of human growth hormone (HGH) in the fetus has elicited some new and surprising findings: two Institute-grantees found that a fetus may begin to secrete and store HGH only 10 weeks after conception, a month earlier than previously believed. And even more surprising, the two investigators found significant HGH in anencephalic fetuses. This is an unexpected finding, since HGH synthesis is thought to be monitored by the hypothalamus and the pituitary gland, and their normal connections to the brain are missing or disrupted in the anencephalic fetus.

The investigators, Drs. Selna L. Kaplan and Melvin M. Gaumbach of the University of California Medical Center, San Francisco, studied 15 aborted but otherwise normal fetuses of gestational ages ranging from 71-223 days. They found that fetal HGH was greatly in excess of the concentration of HGH in pregnant women at comparable stages of gestation, indicating a lack of fetal-maternal HGH exchange. This suggests that the fetus is responsible for the manufacture of its own HGH.

These results, say the investigators, raise important questions about the role of HGH in the fetus and about the control of synthesis of this important hormone.

Rh Blood Disease

The death of a fetus or newborn can result when incompatibility of certain blood subgroups occurs between mother and infant. A major incompatibility involving the Rh blood factor can result in the excessive destruction of the infant's red blood cells shortly before or after birth. This condition, caused by sensitization of an Rh-negative mother by a previous Rh-positive fetus, can be alleviated by exchange transfusions shortly after birth. However, research has developed an anti-Rh preparation by which it is possible to prevent this problem.

This preparation is designed to prevent the Rh-negative mother from becoming sensitized by her baby's Rh-positive blood. Sensitization does not occur until some weeks after an Rh-negative woman has been exposed to Rh-positive blood and may not occur until after several exposures. This new preparation is given within a few days after an Rh-negative mother has given birth to an unaffected Rh-positive baby--before she is sensitized but after she has been exposed to the Rh factor.

The preparation is a highly concentrated solution containing immunoglobulins which contain Rh antibodies. The immunoglobulins are obtained from the blood of Rh-negative women who have been already sensitized to the Rh factor.

This preparation confers a passive immunity which blocks the mother's recognition of the Rh factor, and her immune mechanism does not produce its own Rh antibodies against the baby's blood. The precise mechanism of this immunosuppressive action is not known. However, application of this technique in a large number of cases has been very successful.

Drs. Vincent Freda and John Gorman of Columbia University College of Physicians and Surgeons recently reported the results of such therapy in a patient population of 1,119. Of a combined total of 582 protected mothers, 72 have delivered an unaffected Rh-positive baby. Of 537 unprotected, control mothers, 64 have given birth to Rh-positive babies, of which thirteen were Rh-affected.

These results clearly indicate that the anti-Rh immunoglobulin preparation works exceedingly well. Whether or not the same degree of effectiveness (i.e., 100%) achieved in the postpartum period will persist throughout a subsequent Rh-positive pregnancy cannot yet be said. Thus far, the results are encouraging for a subsequent pregnancy.

This preparation, which is now being reviewed by the Division of Biologics Standards, may soon become generally available as a public health measure for the prevention of Rh hemolytic disease of the newborn.

Effect of Environmental Factors on Birth Weight

The assumption that racial or genetic difference accounts for variation in birth weight in different ethnic groups has been challenged in the years since the end of World War II. Evidence collected mainly on Japanese women has indicated that socioeconomic factors are at least partially responsible for variations in birth weight. Whether increase in average birth weight after improvement of economic and health conditions is due to increasing length of gestation or better fetal growth is not known.

Dr. Peter Gruenwald, Sinai Hospital of Baltimore, Maryland, in collaboration with a team of Japanese obstetricians and pediatricians, has made a study of the hospital records of three large Japanese obstetric services to determine the relation of birth weight to gestational age. The records studied covered a 20-year period in which recovery from wartime deprivation took place and the mean birth weight increased over prewar levels. Weights for the latter part of the third trimester of pregnancy showed a striking increase during the 20 years. There was no significant increase in gestational age. The results suggest a prominent effect of socioeconomic factors on fetal growth. These studies do not negate, however, the existence of some genetic effects.

These findings also support an earlier study by Dr. Gruenwald in which he suggested that human populations with similar adult stature follow a similar prenatal growth curve up to about the beginning of the last

trimester. Beyond this time factors such as maternal undernourishment have a greater effect on fetal growth. Thus, during the unfavorable postwar conditions of 1945-46, growth support of the Japanese fetus was sufficient to assure normal growth up to 35-36 weeks. In the more prosperous 1963-64 period, normal growth was supported up to 38 weeks. Evaluation of growth in the next few years may show that the growth curve of the Japanese is not significantly different from that of Western Europeans.

Carbohydrate Metabolism in Neonates

A lower than normal blood sugar level (hypoglycemia) has been reported in the infant of low birth weight relative to duration of pregnancy. This is especially true in the smaller member of twins. Drs. R. S. Pildes, A. E. Forbes, and M. Cornblath of the University of Illinois College of Medicine, Chicago, found that hypoglycemia occurred frequently and primarily in twin pairs in which there was a greater than 25 percent difference in weight and the smaller infant weighed less than four and one-half pounds.

Since it is known that hypoglycemia can cause severe brain damage if left untreated, these investigators propose that frequent blood samples for glucose should be obtained, especially during the first 24 to 48 hours after birth, in the smaller of two markedly discordant twins. Immediate treatment of the symptomatic hypoglycemia is critical. Lower mental abilities in the smaller of twins has been attributed to hypoglycemia.

Diagnosis of Congenital Deafness

The diagnosis of congenital deafness in infants is a practical problem for the pediatrician. It is important that this diagnosis be made early to prevent later disorders of speech acquisition and language development.

Institute grantee Dr. Ann B. Barnet, working at the Children's Hospital in Washington, D.C., has developed a new technique for diagnosing congenital auditory defects. Computer analyzed EEG responses to clicks, tones, and light flashes revealed deafness in 12 of 22 infants 1-8 months old whose mothers had rubella during pregnancy. The results of the EEG testing correlated highly with additional clinical and behavioral evaluations.

This new method of diagnosing deafness in infancy can be a valuable aid to the pediatrician. With better diagnostic techniques, earlier rehabilitation of the deaf child is possible, giving him a better chance for normal speech and language development.

Sensory Deprivation, Impoverished Environments, and Brain Damage

An Institute grantee has found that early sensory deprivation may cause structural changes in the brain which can result in later defects in learning abilities.

In a study of the effects of visual sensory deprivation in rabbits, Dr. Arnold B. Scheibel of the University of California School of Medicine, Los Angeles, found that the structure of neurons in the visual cortex was significantly altered by depriving experimental animals of light.

Nineteen rabbits raised in complete darkness were sacrificed at 30 days of age. Analysis of the visual cortex using rapid staining and careful counting techniques showed marked changes in the appearance of dendritic spines, parts of the brain structure assumed to be important for proper perception. These physiological changes in the brain stemmed directly from the lack of visual stimulation.

These findings suggest that impoverished environments lacking in certain kinds of sensory stimulation may lead to "brain damage" which can lead to later defects in perception and difficulties in learning.

Individual Serum Cholesterol Levels During Growth

Data on changes in amounts of serum cholesterol in normal children and adolescents have been obtained through a longitudinal study by Dr. Virginia A. Lee of the Child Research Council, University of Colorado School of Medicine, Denver, under support from the Institute. These data shed new light on the changes which occur in the cholesterol level of the growing child and the relation of these changes to subsequent adult cholesterol levels.

Previously, cross-sectional studies indicated that average serum cholesterol of children did not change appreciably from one year to another during the years of growth and was lower than that reported for adults. However, in her longitudinal study of children over a 10-year period, Dr. Lee found patterns of change not evident in the cross-sectional studies.

Dr. Lee measured the total serum cholesterol of 35 boys and 28 girls, aged 4-18, at 6-month intervals over a period of 10 years. She noted modest variations in both sexes during the childhood years (4 to 10 years), and an increase of 5-16 percent in half of the boys during the preadolescent period (10-12 years), but no comparable change in the girls at this age. The most remarkable change, however, appeared during adolescence: cholesterol levels decreased in 80 percent of the 30 individuals studied during this period. These decreases were related to the height of the cholesterol at the start of adolescence, with those children having higher initial levels showing a greater percentage decrease.

These findings establish useful baseline data for future cholesterol studies and provide some understanding of the relationship of childhood and adult levels of cholesterol. They also underline the contributions of longitudinal research projects--which measure changes in single individuals over an extended period of time--to the understanding of the body processes.

Growth Retardation and Hormone Balance

Influences of other hormones on the activity of growth hormone provide intriguing research problems for investigators interested in growth retardation. Scientists know that hormones such as estrogen and the corticosteroids, although present in the body normally, retard growth when administered to children in large amounts in prolonged treatments. However, the mechanisms through which these hormones act to stunt growth remain unclear.

But two Institute grantees have come up with some answers:

At the Children's Asthma Research Institute and Hospital in Denver, Dr. Jacqueline Jorgensen and Dr. Helen Morris studied a group of asthmatic children whose growth had been stunted by prolonged treatment with corticosteroids. These children were severely affected with asthma and thus required the corticosteroids for control, in spite of the damaging side effects. They found that the corticosteroids appeared to inhibit growth by interfering with the metabolic action of growth hormone in the body, and not by blocking its production or release. The steroid-treated children showed the same plasma levels of growth hormone as a group of normal untreated controls. However, upon administration of growth hormone, the investigators did not observe the metabolic or growth changes found in the control groups of untreated asthmatics.

Dr. Antonio Pecile of the University of Milan, Italy, has found that estrogen treatment, on the other hand, interferes with growth by blocking the production of growth hormone by the pituitary gland. It does not appear to interfere with release of the hormone. In a study with rats, Dr. Pecile found a decreased pituitary gland content of growth hormone in animals treated with estrogen as compared to a group of non-treated controls. Discontinuation of estrogen produced a return to normal growth hormone levels in the pituitary gland, and a resumption of normal growth.

These findings contribute to an understanding of how growth is affected by the body's hormone balance. They are basic to developing methods for avoiding growth inhibition in children treated with hormones and are important to understanding processes of normal growth and development.

Normal and Abnormal Growth

The first scientific measurements of "recovery growth" following correction of congenital heart defects in children have been established by Dr. Donald B. Cheek at Johns Hopkins University, under a project supported by the Institute.

Children with congenital heart disease are often stunted in growth when compared to normal children. However, a period of rapid catch-up growth usually follows correction of the defect. Previously, this growth could be measured only in terms of height and weight. By measuring the components of body composition, such as cell volume, distribution or water in the body, muscle cell growth, amount of fat, and amount of lean tissue, Dr. Cheek and his co-investigators have been able to learn more about how these children grow.

This research is part of a unique multidisciplinary program on the study of human growth. Researchers in this program have noted differences in muscle cell growth in boys and girls, with the size of cells growing more rapidly in girls, but reaching their maximum size at a much earlier age. Muscle cell number, however, increases more rapidly in boys than in girls.

In work with hormones, the investigators have found that growth hormone promotes growth mainly in the number of cells, while insulin is more important in the growth of the size of the cells.

Research findings from this project have recently been published in a book, Human Growth: Body Composition, Cell Growth, Energy and Intelligence, compiled by Dr. Cheek, which covers normal and abnormal human growth from various viewpoints, including the whole body level, the tissue level, and the cellular level.

Some of the basic aspects of growth which this book explores are the relative importance of increase in cell size versus the increase in cell number, the relationship of cell mass to growth, and the phenomenon of biological age. Researchers in the fields of biochemistry, endocrinology, cardiology, physiology, and psychology participated in this collaborative project. Thus, the book supplies comprehensive information from multiple disciplines relating to the same group of children.

Children's Attitudes Toward School

Schools themselves may be a major cause of the negative attitudes of culturally disadvantaged children toward education.

Institute grantees, Drs. Daniel C. Neale and John M. Proshek, working at the University of Minnesota, have found that culturally deprived children

appear to value school--and school books--highly, at least at the beginning of their school careers, but that their attitudes toward school become increasingly negative with time. In the study, the same phenomenon occurred in a group of middle class controls.

The two investigators studied 350 children in the 4th, 5th, and 6th grades of two elementary schools--one low, according to socioeconomic indicators, the other near the average. Both groups displayed positive attitudes toward school in general, but the "deprived" children evaluated things such as "my school books," "my school building," and "having to keep quiet" more highly, while the "average" students showed more favorable attitudes toward such school aspects as "my teacher" and "college student." But as grade in school increased, evaluations of all these aspects became less positive for both groups.

These findings suggest that schools are failing in one of the most important objectives of education, that of maintaining a positive attitude toward school by the students.

Performance and Motivation

Determining what may motivate the mentally retarded child to carry out various activities is particularly relevant to research on the learning and performance of these children. This is because when intellective factors are limited in the individual, there is an increased necessity and opportunity for bringing to bear appropriate "nonintellective" factors to influence performance.

Institute-supported researchers, Drs. H. Carl Haywood and S. Joseph Weaver of the George Peabody College for Teachers, Nashville, Tennessee, have assessed how individual motivational orientations affect the vigor with which mentally retarded subjects perform simple motor tasks.

Eighty subjects, divided into intrinsically motivated and extrinsically motivated groups on the basis of pretesting, participated in this project. Forty were intrinsically motivated--achieving main satisfaction through the actual performance of tasks (task content)--and 40 were extrinsically motivated--obtaining main satisfaction from the ease, safety, comfort, security, and material rewards of the environment (task context). Subjects were selected from the Southbury Training School, a residential facility for the mentally retarded in Southbury, Connecticut.

They were given the task of punching holes in specially prepared answer sheets with a metal stylus. Each of five columns on the answer sheet contained 210 circles. The subject's task was to punch as many holes as he could, each one through a printed circle on the answer sheet, during a 30-second trial. At the conclusion of each of four trials he received either 1¢, 10¢, another task, or no reward.

Those who received 1¢, 10¢, or no reward were told to punch holes again. The task given as a reward was the more interesting job of drawing as many circles (or triangles, or triangles-in-circles) as possible before the instructor said stop.

This study showed that the intrinsically motivated subjects performed better under the promise of another task than they did under material (money) or no reward (control) conditions. The extrinsically motivated subjects punched more holes under the money incentives than under either of the other two conditions.

This finding could have major implications in working with the retarded in educational or work settings where completion of one task ordinarily leads to another. In these settings, few material rewards are forthcoming immediately after the first task, and material reinforcement usually must wait for report card time or payday. The investigators report that delayed material reward may have less effect on the level of task-to-task performance of retardates than was previously thought, while personality and motivational factors may have more effect.

Improving Learning Ability

As people age, their ability to learn, especially within a limited time, decreases. Investigators at the Gerontology Research Center in Baltimore have found verbal learning capacity improves in aging individuals who read aloud or make the correct response while learning.

At the Center, learning ability has been studied since 1960 using the paired-associate technique, where new associations, e.g., between letters and numbers, are learned, similar to learning vocabulary in a foreign language or learning a code. Each item to be learned consists of a stimulus and a response. First the participant is instructed to give a response when the stimulus is presented alone. This is followed by the entire item, stimulus and response, to confirm or disconfirm the participant's response.

The investigators hypothesized that for the old person, the probability of responding correctly is related to learning; i.e., the higher the proportion of correct responses, the better the old subject would learn.

To test this hypothesis, they used prompting; i.e., the stimulus was first presented together with the response; then the stimulus appeared alone. The participant had just seen the response with its stimulus and was quite likely to say the response when he saw the stimulus alone. The investigators found that the high percentage of correct responses during this type of prompted learning decreased the learning deficit in older subjects.

It has been shown that learning performance is improved in old persons who respond frequently during the learning situation. This year, the investigators tested the possibility that overt responses serve as auditory stimuli which improve the likelihood of the response being retained. The study was designed to test learning performance under three different input conditions: visual only, visual with passive auditory (given by the experimenter), and visual with active auditory (given by the participant). They found that adding an auditory input to the visual input did facilitate short-term retention for the old. There appeared to be some small additional effect of active responding over and above the effect of auditory input.

Why should learning and short-term retention improve for the old person when he says the material aloud or when the material is presented aloud? Evidence from several psychology laboratories indicates that material presented visually in short-term retention is converted to an auditory storage, and if auditory storage does not occur, at least under some conditions all the material is forgotten in a fraction of a second. The principal investigator of the Gerontology Research Center study, Dr. David Arenberg, believes the old have difficulty converting visual input to auditory storage. Therefore, any aspect of the learning situation that facilitates this conversion to auditory storage, such as active responding or auditory presentation, should be particularly beneficial to the old person's learning and retention. All of the results of this study are consistent with this view.

Chromosome Studies

Chromosomes are structures deep within living cells that contain the complete design for the living organism. Normally humans have 23 pairs of chromosomes. One pair are sex chromosomes and the remaining 22 pairs are called autosomes and control the many other characteristics of an individual.

Since 1959, when it was discovered that chromosome abnormalities are linked to mongolism (Down's syndrome), there has been a growing interest in human cytogenetics--the branch of genetics dealing with the study of cells. Laboratories throughout the country are studying the relation of cell structure and function, seeking to develop methods for detecting chromosome abnormalities that may lead to death, disability, or such conditions as mental retardation.

Recently the importance of performing cytogenetic studies was brought out with the discovery of the first known case of a child who survived with one autosome missing. Until this finding, it was not clear whether a missing autosome was incompatible with extrauterine human life.

The discovery was made by a team of specialists from the Children's Diagnostic and Study Branch and the Laboratory of Biomedical Sciences, both part of the Institute. While evaluating a 4½-year-old mentally

retarded girl, the team's cytogeneticist determined that one of her chromosomes in the 21-22 group was missing. The investigators conclude that the lethality of a missing autosome must depend on the particular aspect of development that the chromosome controls. So far, the scientists have not linked specific abnormalities with the missing chromosome but their continuing studies may eventually determine its role.

In this study there were no unusual findings in the child's heredity or in the mother's pregnancy to indicate a cause for the missing chromosome. Upon close examination some physical abnormalities were noted, including: wide-set eyes with a downward and outward slant; flared nostrils; small, low-set ears; and short, spade-like hands. She also had a minor problem in coordinating and moving the limbs on the left side. Psychologically, most of her mental ability measured in the two-year range with language skills undeveloped.

Metabolic Defects

Galactosemia is an inborn error of carbohydrate metabolism characterized by growth failure, cirrhosis of the liver, cataracts, and mental retardation. It is due to the lack of an enzyme--galactose-1-phosphate uridyl transferase--which is necessary for the normal metabolism of dietary galactose. Galactosemic infants treated promptly with a galactose-free diet usually develop normally, but if the diagnosis of galactosemia is delayed, permanent damage results.

Unlike phenylketonuria, another metabolic disorder for which extensive screening programs are already under way, the large-scale screening of infants for galactosemia had not been reported before 1967, although two methods employing radioactive galactose had been suggested.

Now the recent development of two more methods for detecting the enzyme deficiency in whole blood makes it possible to screen directly for the enzyme defect at low cost and without the use of radioactive reagents. Recently scientists supported by the Institute carried out field tests on these two new screening methods and found them acceptable and in every way highly satisfactory for mass galactosemia screening.

These researchers, Ernest Beutler and four colleagues from the City of Hope Medical Center in Duarte, California, carried out their screening on 15,000 newborns in county hospitals, health plan hospitals, and private hospitals in their State.

Using minute amounts of blood from subjects, the investigators employed the new methods--one a methylene-blue linked test, and the other a fluorescent spot test--for their field trials.

Very generally, in the methylene-blue method, the infant's whole blood is put into a special dye solution. If the enzyme galactose-1-phosphate uridyl transferase is present, a series of chemical reactions occur which change the solution from dark blue to bright red. In the fluorescence spot method, the blood is placed in a different solution. If the enzyme is present, it will attach to a coenzyme in the solution to form a substance which will show under ultraviolet light.

The investigators found no galactosemia in the 15,000 infants screened during their field trials. This is not surprising, since the incidence of galactosemia is estimated to occur in 1 infant out of every 25,000-30,000 born.

The California scientists' trials did show, however, that either of the new screening methods described can be employed effectively to screen for galactosemia in newborns. They also found that the fluorescent method was faster, with one technician able to carry out 125-175 screening procedures a day as compared to only 50-65 in the methylene-blue linked method.

The researchers noted that both tests work best when whole blood from infants is used but will also work adequately when dried blood on filter paper is used, as in screening for phenylketonuria. Therefore, institutions carrying out screening for phenylketonuria could also probably screen easily for galactosemia with little additional effort or expense.

Another metabolic defect resulting from the absence of an enzyme received considerable attention in 1967 when the Institute helped sponsor a working conference on the Lesch-Nyhan syndrome.

This syndrome, first described in 1964, is associated with either mental retardation or neurological symptoms. It appears in early infancy and is characterized by progressive choreoathetosis or spasticity as well as aggressive self-mutilization of the lips and fingers by biting. It is a sex-linked, familial condition associated with high levels of uric acid in the blood and the lack of an enzyme important to purine metabolism. This syndrome is the first example of a link between a specific enzyme defect and abnormal compulsive behavior.

At this first, large-scale conference, 33 scientists concerned with the defect met to review current work in this area and to suggest tentative research approaches. Topics discussed included the syndrome's etiology; possible means of early detection or prevention; broad social implications of the disease as it relates to aggressive human behavior; and whether mental retardation is a true manifestation of this syndrome.

Mucopolysaccharides of Connective Tissue

The aim of Dr. Karl Meyer's study at Yeshiva University Medical School in New York City is to explain the biological roles of the main groups

of the mucopolysaccharides (complex sugar molecules with attached amino sugar and uronic acid groups) of connective tissue.

One of the most striking events in the maturation and aging of the skeleton are alterations in the quantity and distribution of the mucopolysaccharides. The relative concentration of keratosulfate increases, while other mucopolysaccharides decrease. This research is trying to determine the structure and function of keratosulfate and other mucopolysaccharides, as well as their possible relationships to some inheritable diseases; e.g., Marfan's syndrome (characterized by skeletal abnormalities) and Hurler's syndrome (characterized by dwarfism and mental retardation).

The studies in this laboratory have led to the following data: 1) Keratosulfates are a family of similar but distinctly different compounds. 2) All keratosulfates are bound to specific proteins by strong chemical bonds. The nature of these bonds has been determined. 3) Keratosulfate is highly increased in tissues of patients with Marfan's syndrome, and it lacks the cross-linkages present in normal skeletal keratosulfate. 4) The structure of a portion of the keratosulfate molecule in old human rib cartilage recently has been determined.

Effects of Diet

Dr. Morris Ross, a grantee at the Institute for Cancer Research in Philadelphia, studying the effects of diet on life span, on liver and kidney function, and on tumor incidence in the rat, has found that:

1) When the experimental dietary regimen, consisting of diets varying in their proportions of proteins, carbohydrates, and fats, was begun at weaning (21 days in the rat), significant extensions in life span were observed for rats fed a diet with a protein/carbohydrate ratio of 1/5, and whose intake was restricted. When the diet was offered to mature rats in limited amounts, life expectancy was significantly increased. However, mature rats eating all they liked of the experimental diets showed a decrease in life expectancy.

2) A restricted intake of protein, carbohydrate, or both reduced the incidence of progressive glomerulonephrosis (PGN), a major kidney disease in some strains of rats. Carbohydrate restriction produced the best reduction in PGN. PGN reduction was not directly related to the level of protein intake.

3) Activities of several liver enzymes were correlated with various diets: e.g., the activity of alkaline phosphatase, which plays an important role in bone formation and carbohydrate metabolism, correlated directly with rate of change in body weight, regardless of protein, carbohydrate, or fat content of the diet.

4) Calorie and protein intake modify tumor incidence patterns in the male rat. Total tumor risk was directly and exponentially related to caloric intake, but time differences for development of each of the incidence patterns were related inversely to caloric intake. Within each dietary group, rats of heavier weight had greater tumor risks than lighter rats. Altering protein intake altered the type of cancers that predominated. Lowest incidence, greatest delay in time of occurrence, absence of malignant epithelial tumors and greatest life expectancy were observed in underfed rats, whose intakes of protein, carbohydrate and total calories were low.

Decline in Organ Performance

At the NICHD's Gerontology Research Center in Baltimore, 600 men, young and old, are undergoing examinations every 18 months for the rest of their lives, with the aim of revealing aging trends in the individual subjects. This collection of data, now in its tenth year, is beginning to yield interesting information both about changes in the individual with age and differences between people of various ages.

In the past year, performance of two organ systems was shown to decline more with age than performance of components of the systems. For the pulmonary system, changes in the vital capacity of the lungs (VC) (i.e., the greatest volume of air the lungs can expel after a maximum inspiration) have been recorded over a six-year period in young and old subjects in the longitudinal study. Average decline in function was the same for all age groups. However, on the task of using the pulmonary components to demonstrate maximum breathing capacity of the lungs (MBC), older subjects showed a significant decline in performance not evident among younger men. MBC, the greatest amount of air that can be voluntarily breathed during a 10-30-second period, is a reliable test of the ventilatory capacity of the lungs.

Changes in muscular system performance with age were analyzed by comparing young and old subjects with each other rather than with their own previous performances. The complex task performed was rotary crank-turning with the arms; the component tested was muscle strength of the arm and shoulder. Subjects were from the longitudinal study and ranged from 20-89 years old. The average composite strength score for the arm and shoulder declined from 150 in 20 to 69-year-olds to 130 for men in their seventies and 105 for men in their eighties. However, cranking ability began to decline at age 40 and declined progressively through age 89. In addition to beginning earlier, the amount of decline was greater (30%) for manual cranking ability than for strength (20%).

In both organ systems, the need for coordination ability to perform the more complex task seems to have put the older person at a disadvantage which would not have been predicted from the measurement

of the potential (VC or strength) of the lungs or arms. These studies point to a principle that will be tested further at the Gerontology Research Center: that the overall change in a system may be greater than the sum of the changes in the individual components of the system.

Infectious Diseases

A new Institute publication, The Prevention of Mental Retardation Through Control of Infectious Diseases, sets forth definitive information on the role of one set of agents in the cause of mental retardation and should help expand research on this important problem as well as provide guidelines on how best to implement presently available knowledge.

The book comprises the proceedings of the first of seven conferences planned by the NIH and other units of the Department of Health, Education, and Welfare to deal with special research problems underlying mental retardation. Such conferences were recommended by the President's Panel on Mental Retardation in its report of 1962.

In addition to a discussion of the various infections which cause mental retardation--encephalitis, measles, whooping cough, vaccinia, poliomyelitis, scarlet fever, toxoplasmosis, rubella, meningitis, and mumps, among others--the discussants considered how infections might be prevented and treated and how damage to the central nervous system might be elucidated, measured, and possibly some day repaired.

A major problem in studying the role of infectious diseases in mental retardation is the difficulty in linking the infection with the damage to central nervous system. Mild infections, especially viruses, may cause severe mental retardation in later years. On the other hand, many cases of encephalitis, for example, occasionally result in an apparently serious deficit which later disappears. Furthermore, mild forms of mental retardation occur much more frequently than severe deficits, yet there are almost no data available to indicate the relationship of infectious agents to these less severe cases.

The complex problem of prenatal infections was discussed in some detail. Rubella and cytomegalic inclusion disease, toxoplasmosis and syphilis are the four diseases known to cause mental deficits in some offspring. A wide variety of other agents, however, need more study to clarify their relationship to mental retardation.

Finally, the conferees discussed social factors which determine not only the frequency of such an illness but also the outcome and consequences. Many of the participants commented on the fact that there is a remarkable correlation between the incidence of mental retardation and adverse social, economic and cultural environment. Those conditions associated with a high incidence of infectious diseases and with other health and social problems are, to a large extent, the same ones involved in the problem of mental retardation.

The new volume contains recent advances in the field, identifies new areas for scientific exploration and delineates ways to promote the application of known techniques for preventing and treating infectious diseases which may lead to damage of the central nervous system. Hopefully, the book will serve as a springboard for expanding research and cooperation among scientists concerned with infectious diseases and mental retardation.

## MORTALITY AND MORBIDITY FROM CANCER

Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute

Statistics of the annual number of deaths and total current number of disabilities caused by the major diseases dealt within the National Cancer Institute.

I. Cancer deaths in 1966 (Estimated data in Provisional Report of the National Center for Health Statistics, Division of Vital Statistics):

| | |
|---|---|
| Buccal Cavity | 6,120 |
| Digestive system | 94,770 |
| Respiratory | 55,450 |
| Breast | 27,420 |
| Genital organs | 40,480 |
| Urinary organs | 14,110 |
| Leukemias | 14,080 |
| Lymphomas | 15,370 |
| Other sites | 35,500 |
| Total, all sites | 303,300 |

II. Cancer disability in 1966 (estimated on the basis of data supplied by the National Cancer Institute and the National Center for Health Statistics):

(a) Estimated cases under treatment..... 917,000
(b) Estimated person-days of disability (these estimates have a large margin of error):
Restricted activity.....61,714,000
Sick in bed.....34,938,000

III. Cancer's cost to the Nation in 1963 (Source--Estimating Cost of Illness - Health Economics Series - No. 6. These figures refer to all neoplasms - benign, malignant and unspecified.)

(a) $1.3 billion were spent for direct costs, hospital care, nursing home care, physicians' services and nursing services for neoplasms.

(b) A total of 153,000 man-years of productivity, amounting to $850.7 million, were lost in 1963 as a result of illness and disability for members of the labor force, housewives, and others who were alive but unable to attend to their usual activities because they had cancer. The loss was far greater for persons who had died of cancer, but might otherwise have still been alive and productive.

(c) Total economic costs which include estimated direct expenditure, indirect cost of morbidity and present value of life time earnings amounted to approximately $9 billion.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Heart Institute

## CARDIOVASCULAR DISEASES

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the National Heart Institute, and the estimated annual cost to the Nation:

I. Deaths from cardiovascular diseases during 1966 (Vital Statistics of the United States, 1966, Vol. II, Part A, in preparation, Division of Vital Statistics, National Center for Health Statistics):

| Category: | Number |
|---|---|
| Arteriosclerotic heart disease (include coronary disease or "heart attacks") | 573,191 |
| Cerebrovascular lesions (includes strokes and other blood vessel diseases in the brain) | 204,841 |
| Hypertension | 65,556 |
| Non-rheumatic chronic endocarditis and other heart muscle degeneration | 53,581 |
| General arteriosclerosis | 38,907 |
| Rheumatic fever and rheumatic heart disease | 15,012 |
| Other cardiovascular diseases | 59,724 |
| Total | 1,010,812 |

II. Disabilities from cardiovascular diseases (unpublished figures from Division of Health Interview Statistics, National Center for Health Statistics, based on data collected during the period July 1966 to June 1967).

| | Disability Category | |
|---|---|---|
| | Restricted activity | Bed disability |
| Average annual number of disability-days (in millions): | | |
| Cardiovascular conditions | 452 | 160 |
| Heart conditions | 206 | 73 |
| High blood pressure a/ | 66 | 17 |
| Other cardiovascular conditions | 180 | 70 |
| Average number of persons (in thousands): | b/ | b/ |
| Cardiovascular conditions | 1,238 | 437 |
| Heart conditions | 565 | 199 |
| High blood pressure a/ | 180 | 46 |
| Other cardiovascular conditions | 493 | 192 |

a/ without heart involvement
b/ disability days/365

III. Estimated annual cost to the Nation:

A. Estimated economic impact (Health Economic Series Number 6, Estimating the Cost of Illness, USPHS, DHEW, May 1966).

The total economic impact of cardiovascular (including cerebrovascular) diseases on the Nation was estimated at $28.2 billion for the year 1965. This figure includes:

| | |
|---|---|
| Direct costs (hospital and medical services)... | $4.2 billion |
| Indirect costs (non-productivity): | |
| From illness during 1965..... | 3.6 billion |
| Discounted future earnings of persons who died in 1965..... | 20.4 billion |

B. Veterans compensation and pension payments (Unpublished data from Veterans Administration)
Payments to veterans (primarily World War I) disabled by diseases of the circulatory system are estimated to total $593 million for the fiscal year 1967.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Institute of Dental Research

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the Dental Institute, and the estimated annual cost to the Nation.

1. Deaths related to dental disease
   No information available.

2. Disabilities caused by dental diseases.

   Dental caries is the most prevalent disease affecting man. Although new preventive measures have greatly reduced the amount of tooth decay in certain areas, the neglect of dental caries represents the major cause of tooth loss during the first three decades of life. Further, the physical trauma incident to the extraction of decayed teeth can have severe consequences on individuals suffering from certain kinds of heart disease as a result of the introduction of harmful bacteria into the bloodstream. In addition, the early loss of teeth from decay contributes significantly to impaired speech and mastication, and to malocclusion which may eventually predispose to destructive diseases of the supporting structures of the teeth.

   Periodontal disease is the leading cause for tooth loss in persons over 34 years of age. It affects almost everyone sooner or later, eventually causing far more loss of teeth than does dental decay. A report from the National Center for Health Statistics in 1965 revealed that, among the 90 million adults in the United States with teeth, only one out of four exhibited no signs of periodontal disease. Another study showed that periodontal disease is responsible for about 65 percent of extractions in adults in the fourth decade of life. Conservatively estimated, about 20 million Americans are without teeth or require removal of all their teeth due to advanced periodontal disease.

   Today, over a quarter of a million persons in the United States have some form of oral cleft, and each year one out of every 750 babies is born with a cleft (hare) lip or cleft palate or both. Some 6,000 babies were born with this abnormality during 1966. Cleft lip/palate make up 13 percent of all reported birth anomalies. Without proper therapy, afflicted persons go through life with deformed noses, scarred lips, mutilated palates, and incoherent speech. Successful rehabilitation of the cleft palate child requires the solution of a series of complicated clinical problems through the coordinated efforts of many specialists, including orthodontists, prosthodontists, plastic surgeons, otolaryngologists, psychologists, speech therapists, and social workers.

Cancer of the mouth accounts for approximately 4 to 6 percent of all cancers occurring annually in the United States. It can occur in men and women of any age, but most frequently is found in men after the age of forty. The most common sites of oral cancer are the lip, tongue, and cheek. Others are the floor of the mouth, gums, palate, tonsils, lower jaw, and salivary glands. Malignant tumors of the mouth cause about 4,000 deaths annually in this country, but more than half of all mouth cancer patients are alive five years after treatment. Eighty-nine percent of males treated for lip cancer are alive five years later, in contrast with only 30 percent of those treated for tongue cancer. Between 1951 and 1961 oral cancer deaths increased by 29 percent.

Dental research findings frequently have significant relationships to other diseases and disorders. For example, the discovery of a mammalian enzymne which breaks down collagen fibers in periodontal tissues may hold clues to other disabling and prevalent collagen diseases, such as arthritis. Another example: in a study of relationships between the sympathetic nervous system and salivary secretions, a dental investigator has shown that the drug, guanethidine, can improve temporarily the chemical balance of the saliva of children with cystic bibrosis. This is the first available agent to separate two factors--the organic and the calcium components-most readily associated with abnormal saliva in cystic fibrosis cases.

Although the broad program of fundamental research of the NIDR acknowledges major responsibility for resolving the many existing problems of treatment or prevention of oral diseases, more imaginative concepts of objectives are constantly being sought in order to increase basic knowledge of oral biological systems and their interrelationships with the whole body.

3. Estimated annual cost to the nation

The problem of oral disease makes its greatest impact on the American people through its universality and its cost. Very few persons escape it entirely, and it represents 10 percent of the total cost of medical care spent each year. In spite of the huge annual expenditure for dental care, an estimated 60 percent of our people are not availing themselves of dental treatment. These statistics, when coupled with the fact that our population is growing, that more people are living longer, that a new interest in dental care is generated by Medicare and other public education programs, and that dentists are in seriously short supply, leads to a dental public health problem of staggering proportions.

Approximately 3 billion dollars is now being spent annually for dental treatment by a small segment of the population. There is sufficient evidence to suggest that the total annual cost for dental treatment would be in the range of twenty to twenty-five billion dollars for the first year if all individuals needing treatment were to receive it. This initial cost would decrease sharply, but the continuing annual expenditure would still be prohibitive. The burden to individual families may be high especially for such conditions as cleft palate. Although the cost of treatment of cleft palate varies in different regions of the United States, the total direct cost is estimated to range from $5,000 to $15,000 for a single case covering the period from birth to 16 years of age. For either cleft lip or cleft palate the private surgeon's fee alone ranges from $300 to $1,000 per case, depending on the severity of the abnormality. The source of the latest available figures on man-hours lost from productive work during dental visits, the 1964 National Health Survey showed that nearly 3 hundred million dental visits were made by persons in the civilian, noninstitutional population.

## ARTHRITIS AND METABOLIC DISEASES

Statistics concerning the number of deaths and disabilities caused by some of the major diseases under study in the National Institute of Arthritis and Metabolic Diseases, and the estimated annual cost of arthritis to the Nation.

I. Estimates of the number of deaths during 1966 (Source: National Center for Health Statistics, PHS)

| Category: | |
|---|---|
| Diabetes mellitus | 35,380 |
| Gastrointestinal diseases (ulcer of stomach and duodenum, cirrhosis of the liver, gastritis, duodenitis, enteritis, and colitis) | 43,160 |
| Total | 78,540 |

II. Disabilities
(Source: Diabetes and Arthritis Program, Division of Chronic Diseases, PHS, 1967.)

Number of persons in U.S. reporting chronic activity limitation due to arthritis (excluding gout and bursitis) during 1961-63: 3,300,00.

III. Estimated annual economic cost to the Nation
(Source: Diabetes and Arthritis Program, Division of Chronic Diseases, PHS, 1967.)

Arthritis and rheumatism, $4 billion.

February 1968

## Estimated Number and Cost of Neurological Disabilities in the United States

### Introduction

As much as 10 percent of the total population of the Nation may be suffering from disabling neurological or sensory disorders, and an estimated 20 percent of hospital admissions are related to these neurological and sensory ailments. Impairments include brain and spinal cord disorders, speech defects, hearing problems, blindness, and visual disorders. Multiple handicaps are common.

Those affected by chronic long-term conditions are confined more to bed, chair, or home and need more assistance in day-to-day living than the victims of almost all other diseases combined. These conditions include cerebral palsy, mental retardation, strokes, epilepsy, multiple sclerosis, muscular dystrophy, spinal injury, and sensory disabilities including loss of vision, hearing, and language. Although many important developments toward their improvement or control are being made, the vast majority of these problems are still incurable.

### Over 200 Nervous System Disabilities

Less known to the public than other diseases, the neurological disorders are equally devastating. In fact, more than 200 clinical disabilities are associated with dysfunction, disease, or injury of the nervous system, which includes the brain, the spinal cord, and their peripheral neuromuscular connections.

### Mortality Statistics

Neurological ailments caused about 20.9 percent of the total United States deaths in 1965. A Pennsylvania study showed that two of every 1,000 live newborns die of neurological conditions before they are one year of age. Although certain chronic neurological conditions contribute to death, they are often not listed as cause of death. Mortality statistics, therefore, do not portray the full magnitude of the neurological and sensory disease problem. For example, a study by the NINDB-supported Parkinson's Disease Center at Columbia University of death certificates of patients known to have Parkinson's disease revealed that in only 60 percent of the cases was this fact noted on the death certificate.

### Data on Prevalence and Economic Loss

Figures on prevalence and resulting economic loss are also difficult to obtain for various reasons. Because neurological and sensory diseases are not reportable, case finding is difficult. Many

conditions become evident to the individual only after they have progressed to a point of disability. Persons affected by some neurological disorders conceal their handicap (e.g., epilepsy) because of job discrimination and other forms of social nonacceptance. Moreover, diagnosis of neurological disorders is still a problem in certain instances; many cases are incorrectly diagnosed or missed for long periods. Thus, the resulting morbidity statistics and economic loss can only be roughly approximated until more accurate data become available on the total number of persons affected by neurological and sensory impairments, together with the degree of their impairments and age groups.

NINDB's Estimate of the Problem

In the face of present data-collection problems, the National Institute of Neurological Diseases and Blindness can only estimate the range and economic cost of neurological and sensory disability. On this score, it has formulated certain assumptions and drawn on figures from the PHS National Center for Health Statistics, special studies reported in the literature, and figures from the voluntary health organizations.

Government and voluntary agencies recognize increasingly the need for reliable data on chronic impairments among our population. Continuing efforts toward achieving this goal will undoubtedly lead to refinements in the collection, analysis, and dissemination of health statistics. Such information has decided importance in assuring a solution to the vast problems raised by chronic illness.

## Range and Cost of Major Chronic Neurological and Sensory Disorders

February 1968

| Disability Category | Mortality 1/ | Est. Total Cases 2/ | Est. Annual Cost of Care 3/ | Remarks |
|---|---|---|---|---|
| NEUROLOGICAL | | | | |
| Cerebral Palsy | 1,230 | 600,000 | $500,000,000 | National Health Education Committee (NHEC) estimates one-third of the cases are under 21 years of age. United Cerebral Palsy estimates about 25,000 babies are born each year with cerebral palsy; approximately 7 per 1,000 live births (1966). |
| Cerebrovascular diseases (strokes) | 200,827 | 2,000,000 | $440,000,000 4/ | One-third of patients with CV ("strokes") are wage earners under age 65 made unemployable by the residuals of a stroke (Source: NHEC and President's Commission on Heart Disease, Cancer, and Stroke, 1964). |
| Epilepsy | 1,881 | 1,000,000 to 2,000,000 | $750,000,000 | Prevalence and economic loss may be higher because many persons with epilepsy conceal their impairment to avoid job discrimination. Epilepsy is usually a long-term chronic disease; about 80 percent of seizures start in childhood or adolescence (NHEC). In 1965, a total of 13,460 patients with convulsive disorders were institutionalized in State and county mental hospitals, costing approximately $33,113,000 a year for care. (NIMH) |
| Multiple sclerosis | 1,530 | 250,000 | $250,000,000 | MS is a long-term disease affecting mainly persons between 20 and 40 years of age. Cost of care varies markedly, depending on patient's economic ability to afford equipment, drugs, physiotherapy, medical attention, hospital care (where needed) and other expenses involved in this chronically progressive disorder. |

| Disability Category | Mortality 1/ | Est. Total Cases 2/ | Est. Annual Cost of Care 3/ | Remarks |
|---|---|---|---|---|
| NEUROLOGICAL (Cont'd) | | | | |
| Amyotrophic lateral sclerosis | 1,225 | 5,000 to 10,000 5/ | $ 10,000,000 | Amyotrophic lateral sclerosis occurs most often between ages 40 and 60; approximately two-thirds are men in the working force. |
| Muscular dystrophy, other muscle disease | 1,005 | 200,000 | $125,000,000 | Nearly two-thirds of known muscular dystrophy patients in the U.S. are children between ages of 3 and 13. (Muscular Dystrophy Associations of America. Inc.) |
| Parkinson's disease (paralysis agitans) | 3,003 | 500,000 | $400,000,000 | Most patients are 50 years or older. The number of persons with Parkinson's disease who die each year may be 5 times greater than the figure shown, because Parkinson's disease, while not usually in itself a direct cause of death, may predispose those afflicted to other diseases that shorten life expectancy. (NHEC and Parkinson's Disease Foundation) |
| Tumors of brain and other parts of nervous system | 8,020 | 140,000 | $272,000,000 | Brain tumors cause about 40 percent of the deaths resulting from diseases of the central nervous system, exclusive of strokes. They have their peak incidence in childhood and in the fifth decade, with males having a slightly higher incidence than females. |
| Spina bifida and meningocele | 1,323 | -- | -- | Based on recorded live births for 1965, an estimated 11,300 babies are born annually with spina bifida or related birth defects of the central nervous system which, for the most part, are incurable. 6/ |
| Accident & injury to nervous system | 112,000 (estimate) | -- | -- | Accident and injury frequently result in long-term disabling conditions of the nervous system. |

| Disability Category | Mortality 1/ | Est. Total Cases 2/ | Est. Annual Cost of Care 3/ | Remarks |
|---|---|---|---|---|
| NEUROLOGICAL (Cont'd) | | | | |
| Head injuries | 50,000 (estimate) 7/ | 700,000 | -- | No figures available on the number who suffer lifelong impairments of the nervous system due to accident and injury, although statistics show that over 700,000 are bed-disabled for 1 day or more as a result of injury to head or skull. (National Center for Health Statistics) |
| Paraplegia and quadriplegia | -- | 60,000 | -- | From Paraplegia Workshop, November 4, 1966, at Bethesda, Md. - NINDB. |
| SENSORY DISORDERS | | | | |
| Eye disorders: | | | | National Society for the Prevention of Blindness, 1965. U.S. National Health Survey figures for 1964-65. NINDB Fact Sheet prepared by Program Analysis, April 4, 1967. |
| Legally blind | -- | 416,400 | | |
| Partially seeing | -- | 5,390,000 | | |
| Estimated annual cost of medical care (crude estimate) | | | $1 billion | An estimated 76.7 percent of legally blind population in the U.S. is 40 years of age or over. (Table 8, p. 33, "Estimated Statistic on Blindness and Vision Problems," National Society for the Prevention of Blindness, Inc., 1966) |
| Hearing disorders: | | | | In October 1967, 38,391 pupils were enrolled in 736 American schools and classes for the deaf, according to American Annals of the Deaf. Of the estimated 64,000 totally deaf adults, half are assumed to be fully disabled and half partially disabled. Deafness incidence rises rapidly with age. |
| Totally deaf | -- | 71,000 | -- | |

| Disability Category | Mortality 1/ | Est. Total Cases 2/ | Est. Annual Cost of Care 3/ | Remarks |
|---|---|---|---|---|
| SENSORY DISORDERS (Cont'd) | | | | |
| Other hearing impairments | -- | 8,578,000 | -- | Figures on prevalence of vision, hearing, and speech disorders are based on household interviews by the Division of Health Interview Statistics, National Center for Health Statistic in fiscal year 1964-65. These figures cover onl the civilian non-institutional population, and indicate that about one-half of all reported speech defects were among children under age 15. |
| Speech impairments | -- | 1,298,000 (5% of school children) | -- | The two deficits, "hard of hearing" and "speech and hearing" frequently occur together, making it difficult, statistically, to separate these two categories of impairments. |
| Reading disability | -- | 2,500,000 to 5,000,000 | -- | An estimated 5 to 10 percent of all school children have some type of reading disability. |

Total: The commonly accepted estimate is that 10 to 20 million Americans have one or more neurological handicaps; many have multiple handicaps.

REFERENCES

1/ Deaths from neurological ailments during 1965, from the Division of Vital Statistics, National Center for Health Statistics, PHS.

2/ Morbidity estimates, for most specific neurological diseases, not available from Division of Health Interview Statistics. Institute estimates obtained from the respective voluntary associations.

3/ Figures on cost of neurological disorders are estimates only, calculated on the following assumptions:

a. Assume that the annual maintenance of the partially disabled individual costs approximately $500 per year for drugs, physicians' fees, and special management.

b. Assume that the annual maintenance of the totally disabled individual cared for at home costs approximately $1,000 per year.

c. Assume that the annual maintenance of the totally disabled individual cared for in public and private institutions costs approximately $2,000.

4/ $440,000,000 per year according to conservative estimates for direct expenditures for services and supplies for diagnosis, treatment, and rehabilitation of stroke victims. (Report to the President, A National Program to Conquer Heart Disease, Cancer, and Stroke, Vol. 1, Dec. 1964)

5/ ALS Fact Sheet, Amyotrophic Lateral Sclerosis, NINDB.

6/ Spinal Birth Defects, Hope through Research, 1966.

7/ NINDB Accident and Injury Information, NINDB, C&FR, Jan. 1968.

January, 1968

Department of Health, Education, and Welfare
Public Health Service

National Institute of Allergy and Infectious Diseases

Statistics covering the annual number of deaths and reported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases are presented in Table I. Only those deaths and new cases reported by professional health personnel are included.

Table II reports annual disability and estimated cost to the nation's populace of infectious, parasitic, and respiratory diseases.

Table I

| Category | Morbidity 1966 | Mortality 1965 |
|---|---|---|
| I. Parasitic infections | | |
| Amebiasis | 2,921 | 66 |
| Malaria | 565 | 8 |
| Schistosomiasis | 288 (2 states) | * |
| Trichinosis | 115 | 3 |
| Other parasitic infections | 2,313 (not all states) | * |
| II. Bacterial diseases | | |
| Brucellosis | 262 | 6 |
| Cholera | 0 | 0 |
| Diphtheria | 209 | 18 |
| Leptospirosis | 72 | 11 |
| Meningococcal infections | 3,381 | 890 |
| Pertussis (Whooping cough) | 7,717 | 55 |
| Salmonellosis (excluding typhoid) | 16,841 | 87 |
| Tularemia and Leprosy | 317 | 5 |
| Septicemia and Pyemia | * | 2,443 |
| Tetanus | 235 | 181 |
| Tuberculosis | 47,767(new active cases) | 7,934 |
| Typhoid fever | 378 | 6 |
| Strep Sore Throat and Scarlet Fever | 427,752 | 63 |
| Rheumatic Fever, acute (36 states) | 4,472 | 483 |
| Shigellosis (bacillary dysentery) | 11,888 | 99 |
| Venereal diseases (new cases) | | |
| . Syphilis | 126,573 | 2,434 |
| Gonorrhea | 351,738 | 9 |
| Other | 1,294 | 11 |

| | | | |
|---|---|---|---|
| III. Rickettsial diseases | | | |
| Typhus (inc. Rocky Mountain spotted fever) | 301 | | 16 |
| IV. Viral Diseases | | | |
| Chicken pox | 136,149 | (41 states) | 143 |
| Encephalitis (primary) | 2,121 | | 500 |
| Hepatitis | 34,365 | | 707 |
| Herpes zoster | * | | 78 |
| Influenza | * | | 2,295 |
| Measles (Rubeola) | 204,136 | (40 states) | 276 |
| Mumps | 128,295 | (34 states) | 31 |
| Mononucleosis | 7,668 | | 28 |
| Poliomyelitis | 113 | | 16 |
| Rubella | 46,975 | | * |
| V. Fungal Diseases | | | |
| Actinomycosis | * | | 26 |
| Coccidioidomycosis | 847 | (10 states) | 52 |
| Blastomycosis | * | | 29 |
| Cryptococccosis | * | | 62 |
| Histoplasmosis | * | | 74 |
| Moniliasis | * | | 93 |
| Histoplasmosis | 236 | (19 states) | * |
| Ringworm | 4,075 | (19 states) | * |
| VI. Allergic Disorders | | | |
| Asthma | | | 4,520 (Pers. comm., Robert Israel, Ch., Mort. Stat. Br., Div. Vit. Statistics) |
| All other | | | 113 |
| VII. Multiple or unspecified classifications | | | |
| Bronchitis (acute) | * | | 1,004 |
| Emphysema | * | | 15,796 (1964 fig.) |
| Meningitis | 2,691 | (except mening. and tb - 37 states) | 2,363 (except mening.)(see scurce above) |
| Pneumonia | * | | 62,381 |
| Respiratory Infections, acute, upper | 442,854 | (19 states) | 745 |
| Other respiratory diseases | * | | 28,238 (1964 fig.) |
| Gastroenteritis and colitis (age 4 wks. - 2 yrs.) | * | | 1,903 |

* Not reported

Morbidity statistics taken from MORBIDITY AND MORTALITY WEEKLY REPORT, Annual Supplement, 1966, Vol. 15, Number 53, November 1967, Communicable Disease Center, Atlanta, Georgia.

Mortality statistics taken from VITAL STATISTICS OF THE UNITED STATES, 1965, Volume II - Mortality - Part A. (As reported in publication above).

TABLE II

Cost to the Nation's Populace

July 65-June 66

| Item | Acute Condition Group<br>Infectious & Parasitic | Respiratory |
|---|---|---|
| Number of cases | 47,909,000 | 240,069,000 |
| Restricted activity (days) | 197,462,000 | 750,360,000 |
| Bed disability (days) | 103,492,000 | 374,343,000 |
| Work loss (days) | 20,966,000 | 119,980,000 |
| School loss (days) | 43,375,000 | 122,422,000 |
| Work loss (cost) | $487,459,500 | $2,789,535,000 |
| | TOTAL WORK LOST | $3,276,994,500.00 |

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From VITAL AND HEALTH STATISTICS - CURRENT ESTIMATES UNITED STATES, July 1965-June 66, Series 10, No. 37, May 1967, and ACUTE CONDITIONS, Series 10, No. 38, June 1967 (DHEW, PHS, National Center for Health Statistics, Washington, D. C.)

Department of Commerce, National Income Division, Personal Income Section, Average Income of Full-time Worker, 1966. ($5,954 annually. Days lost from work cost based on average of 256 working days a year - thus $23.25 per day).

Personal Communication - Charles Wilder - Health Interview Statistics

Morbidity - July 1966 - June 1967

| | Incidence of acute conditions | Prevalence of chronic conditions |
|---|---|---|
| Tuberculosis, Pulmonary or unspecified | | 445,000 |
| Tuberculosis, Arrested or inactive | | 730,000 |
| Strep sore throat | 4,716,000 | |
| Measles | 1,019,000 | |
| Rubella | 2,259,000 | |
| Chickenpox | 2,280,000 | |
| Mumps | 3,730,000 | |
| Hepatitis, infectious | | 84,000 |
| "Virus" infection, ill defined | 26,249,000 | |
| Tapeworm and intestinal worm infestation | | 1,111,000 |
| Athletes foot | | 722,000 |
| Rheumatic fever, active | | 88,000 |
| Rheumatic fever, inactive | | 1,954,000 |
| Common cold | 109,713,000 | |
| Other acute upper respiratory infections | 28,607,000 | |
| Influenza, digestive | 10,524,000 | |
| Other influenza | 44,858,000 | |
| Pneumonia, except primary atypical | 1,839,000 | |
| Bronchitis, no emphysema | | 3,980,000 |
| Acute or unspecified bronchitis | 3,411,000 | |
| Emphysema, no bronchitis | | 726,000 |
| Bronchitis and emphysema | | 197,000 |
| Other diseases of the respiratory system | 491,000 | |

MONDAY, MARCH 18, 1968.

# DIVISION OF BIOLOGICS STANDARDS

## WITNESSES

DR. RODERICK MURRAY, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
GEORGE A. BRUST, EXECUTIVE OFFICER, DIVISION OF BIOLOGICS STANDARDS
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. LEO J. GEHRIG, DEPUTY SURGEON GENERAL
G. RICHARD CLAGUE, DEPUTY CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 2,281 | 2,353 | 2,432 |
| Positions other than permanent | 37 | 30 | 30 |
| Other personnel compensation | 53 | 49 | 49 |
| Total personnel compensation | 2,371 | 2,432 | 2,511 |
| Personnel benefits | 233 | 248 | 253 |
| Travel and transportation of persons | 95 | 106 | 108 |
| Transportation of things | 9 | 10 | 10 |
| Rent, communications, and utilities | 45 | 51 | 51 |
| Printing and reproduction | 10 | 10 | 10 |
| Other services | 381 | 320 | 325 |
| Project contracts | 1,788 | 2,275 | 2,275 |
| Payments to "National Institutes of Health management fund" | 1,708 | 1,845 | 1,880 |
| Supplies and materials | 899 | 885 | 908 |
| Equipment | 248 | 340 | 171 |
| Subtotal | 7,787 | 8,522 | 8,502 |
| Quarters and subsistence charges | −3 | −3 | −3 |
| Total obligations | 7,784 | 8,519 | 8,499 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 333 | 324 | 329 |
| Full-time equivalent of other positions | 6 | 5 | 5 |
| Average number of all employees | 285 | 283 | 287 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| Biologics standards (program costs, funded) [1] | 6,388 | 8,519 | 8,499 |
| Change in selected resources [2] | 1,396 | | |
| Total obligations | 7,784 | 8,519 | 8,499 |
| Financing: | | | |
| Comparative transfers from other accounts | −805 | | |
| Unobligated balance lapsing | 925 | 130 | |
| New obligational authority (appropriation) | 7,904 | 8,649 | 8,499 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 7,784 | 8,519 | 8,499 |
| Receipts and other offsets (items 11 to 17) | −805 | | |
| Obligations affecting expenditures | 6,979 | 8,519 | 8,499 |
| Obligated balance, start of year | 1,087 | 2,638 | 3,145 |
| Obligated balance, end of year | −2,638 | −3,145 | −3,635 |
| Adjustments in expired accounts | −31 | | |
| Expenditures | 5,397 | 8,012 | 8,009 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 4,549 | 6,674 | 6,700 |
| Out of prior authorizations | 847 | 1,338 | 1,309 |

[1] Includes capital outlay as follows: 1967, $156,000; 1968, $340,000; 1969, $171,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $765,000; 1967, $2,161,000; 1968, $2,161,000; 1969, $2,161,000.

Mr. FLOOD. The committee will come to order.

We have the Division of Biologics Standards of the Public Health Service, and Dr. Roderick Murray, the Director, will make the presentation.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Doctor, I see you have a biographical sketch which we will place in the record.

(The biographical sketch follows:)

PUBLIC HEALTH SERVICE, DIVISION OF BIOLOGICS STANDARDS

BIOGRAPHICAL SKETCH

Name: Roderick Murray, M.D.

Position: Director, Division of Biologics Standards, National Institutes of Health.

Birthplace and date: Christchurch, New Zealand, August 12, 1909.

Education: B.S., University of Witwatersrand, South Africa, 1930; M. Sc., University of South Africa, 1931; M.D., Harvard Medical School, 1941.

Experience: 1956 to present, Director, Division of Biologics Standards; 1949–1956, Assistant Chief, Laboratory of Biologics Control, NIH; 1947–1949, Laboratry of Biologics Control, NIH; 1947, commissioned officer, USPHS; 1946–1947, research fellow, Thorndike Memorial Laboratory, Boston City Hospital; 1942–1946, U.S. Army Medical Corps (major); 1942, assistant residency, Second Medical Service, Boston City Hospital (interrupted by military service); 1941–1942, medical internship, Second Medical Service, Boston City Hospital, Boston, Mass.; 1931–1937, biochemist, South African Institute for Medical Research, Johannesburg.

Association memberships: American Medical Association; American Public Health Association (fellow); American Association of Immunologists; American Academy of Microbiology (fellow).

Special awards, citations, or publications: Cullen Medal, faculty of science,

University of Witwatersrand, 1930; Alpha Omega Alpha; Distinguished Service Medal USPHS, 1965. Thirty-nine publications.

Mr. FLOOD. Please proceed, Doctor.

## GENERAL STATEMENT

Dr. MURRAY. Mr. Chairman and members of the committee:

It is again my privilege to appear before you on behalf of the Division of Biologics Standards. The mission of the Division is the exercise of controls on the safety, purity, and potency of biological products through a system of licensing of manufacturing establishments and of the products, as well as the conduct of research related to these objectives in order that decisions made and actions taken can be based on sound information.

Basically, it is the responsibility of the Division to make recommendations for standards for all biological products such as vaccines, serums, human blood and its derivatives, and like products.

## VACCINE AND SERUM

Mr. FLOOD. What is the difference between a vaccine and a serum? What are the sources of a vaccine?

Dr. MURRAY. They are made from viruses or bacteria and they are either alive or killed. These organisms are isolated from cases of the illness. For instance, polio viruses usually come from people with polio.

Mr. FLOOD. If I had an affliction such as yellow fever you could draw from me a vaccine?

Dr. MURRAY. No. The virus which caused it originally came from insects, or from man, and has been worked with over the years.

Mr. FLOOD. What is a serum?

Dr. MURRAY. It is the fluid part of the blood from an animal that usually has been injected with a vaccine or antigen to increase its resistance.

Mr. FLOOD. You say "human blood and its derivatives." What is a derivative of human blood?

Dr. MURRAY. Such as gamma globulin.

Mr. FLOOD. What is that?

Dr. MURRAY. Some of the proteins present in the blood and containing most of the antibodies.

Mr. FLOOD. You break the blood down?

Dr. MURRAY. To its components, yes.

Mr. FLOOD. What do you mean by "like products"?

Dr. MURRAY. That goes back to the statute and it classifies products that cannot be otherwise defined.

## STANDARDS FOR BIOLOGICAL PRODUCTS

Dr. MURRAY. These standards include written standards, eventually promulgated as regulations, some of which apply to individual products and some to products in general; and physical standards, for example, biological preparations whose properties and qualities have been extensively characterized. The latter are issued to manufacturers and other research laboratories concerned with biologics standardiza-

tion for evaluation with their products, particularly with respect to potency, or strength.

The acquisition of the information needed to develop written standards and the laboratory investigations leading to the development and selection of suitable physical standards are extensive in character and often time consuming. This is particularly true of standards for the tissue-culture-prepared virus vaccines such as polio virus, measles, and mumps which have been developed in recent years.

### MUMPS

Mr. FLOOD. We have heard a lot in the last week about this vaccination for mumps. How long has that been available?

Dr. MURRAY. A vaccine against mumps has been available for a number of years. This was an inactivated vaccine.

Mr. FLOOD. Is it contagious or infectious?

Dr. MURRAY. I imagine it can be transmitted both ways.

Mr. FLOOD. Which is more common?

Dr. MURRAY. Usually by infection. The vaccine that has been talked about lately has been developed from a recently isolated strain of mumps virus which apparently can produce antibodies in man without causing illness.

Mr. FLOOD. I never had mumps but my brother had it. Is this peculiar to males or do females have mumps?

Dr. MURRAY. It is not peculiar to males.

Mr. FLOOD. Is this generally contagious?

Dr. MURRAY. It is transmitted generally by children, from one child to another, and adults who have not had mumps can be exposed to infection from children, but usually, from surveys that have been made in recent times, the adult population is pretty much immune, 60 to 70 percent of the adult population is immune.

Mr. FLOOD. Will it sterlize the male?

Dr. MURRAY. Under some circumstances, yes.

Mr. FLOOD. Is that common?

Dr. MURRAY. I would not say it is too common, but it does occur.

Mr. FLOOD. How serious are mumps?

Dr. MURRAY. Mumps can be serious in childhood because it causes encephalitis.

Mr. FLOOD. What is that?

Dr. MURRAY. An infection of the brain, and it may cause a permanent disability.

Mr. FLOOD. There is a direct connection between mumps and encephalitis, then?

Dr. MURRAY. Yes.

### DEVELOPMENT OF STANDARDS

When a new vaccine against a particular disease appears achievable, it devolves upon the Division to develop standards so that they will be ready at approximately the same time that the product is brought to the final stages of manufacture. This requires considerable research involving most of the component laboratories of the Division, as well as the testing of samples of both experimental and final prod-

ucts. It is necessary during this period to maintain close contact with the manufacturer so that problems relating to standards can be ironed out during the developmental phases. In addition, any clinical investigations conducted by the manufacturers come under review of the Division.

When a manufacturer has decided to market a product which he has developed, he submits a license application to the Division together with samples of the product and results of all tests. Division scientists then review the application and perform tests to ascertain the accuracy of the manufacturer's test results. If the tests fulfill the requirements and the application is in order, the product license is recommended for approval.

In the case of a manufacturer already licensed for other biological products, his production facilities may be inspected as deemed necessary according to the nature of the pending product. In the case of a new manufacturer, production facilities are inspected and the personnel assessed prior to licensing the manufacturing establishment, as well as the product he proposes to market. The establishment is inspected annually thereafter to verify that proper procedures are being followed in manufacturing and testing procedures. Samples and the results of tests performed on each batch or lot of all biological products proposed for marketing must be submitted to the Division by the manufacturer prior to distribution. The Division checks the test results and runs similar tests to insure the quality of the products. Only then is a release for marketing issued to the manufacturer.

Once a product has come into use, its safety and potency must be continuously monitored. The knowledge and skill required to do this also provide a sound basis for consideration of problems associated with newer products as they are developed.

### RUBELLA VACCINE

Mr. FLOOD. What is a rubella vaccine?

Dr. MURRAY. A rubella vaccine is an experimental vaccine being developed at the present time and which will give protection against German measles.

Mr. FLOOD. Why "rubella"?

Dr. MURRAY. Rubella is the technical name for German measles. I think in most languages the name contains the connotation of red.

Mr. FLOOD. A rash?

Dr. MURRAY. Yes.

Mr. FLOOD. Doctor, is there a breakthrough on the horizon?

Dr. MURRAY. I think the breakthrough has probably taken place already. It is now a matter of getting the necessary information to be sure the vaccine can be used on a large scale with safety.

Mr. FLOOD. Would you use it on your children?

Dr. MURRAY. When it is properly manufactured.

Mr. FLOOD. Suppose your daughter were going to have a child. Your daughter 20 years of age tells you she is pregnant. What do you do at that age? She is 3 months pregnant.

Dr. MURRAY. If the rubella vaccine had been available, I certainly would have given it to her before she became pregnant, but not after she became pregnant.

Mr. FLOOD. You would give it to her before she became pregnant?

Dr. MURRAY. Yes; in order to provide protection against rubella.

Mr. FLOOD. Would you give every bride a rubella vaccination?

Dr. MURRAY. I am being cautious now. If a rubella vaccine becomes available, I think, what everybody has in mind is to provide protection to those women who might subsequently become pregnant.

Mr. FLOOD. We are getting in the area of increased illegitimate births. If and when the vaccine is developed would you apply it to every female when she reaches the age of puberty?

Dr. MURRAY. I think so. As time goes on recommendations as to the use of the vaccine would be developed. The actual mode of use would have to be determined by the development of more information in the field.

Mr. FLOOD. How is a vaccine given?

Dr. MURRAY. Usually by an injection. Polio vaccine is given by mouth in the form of drops on a sugar cube.

Two years ago Division scientists succeeded in attenuating the rubella virus. Using this weakened virus they developed an experimental vaccine against rubella or German measles. Infections of this disease during early pregnancy frequently result in spontaneous abortions, stillbirths, or birth of infants with grave defects such as blindness, deafness, heart disease, and brain damage.

Vaccines—and I should insert the word "experimental" vaccines—prepared from this attenuated virus have now been administered to over 500 persons. None of these individuals experienced vaccine-associated reactions; over 90 percent developed protective immunity. Continued observation of the first groups of children vaccinated 2 years ago indicates that the immunity conferred by the attenuated virus will be of long duration. Thus far, the vaccine appears safe as well as effective..

During the past year, Division investigators and collaborating groups have found answers to several questions important to the development of the vaccine. These studies have been concerned with (1) determining the optimum degree of attenuation for a virus strain destined for use in vaccine production, (2) evaluating the characteristics of experimental rubella vaccines produced in various types of tissue cultures, and (3) insuring the maximum practical application of the new rapid blood test (HI test) developed by Division scientists for the detection of rubella immunity and determination of the protective antibody response in vaccinees.

During the coming months the Division will be involved with groups conducting progressively larger rubella vaccine field trials and will continue to keep in close contact with rubella vaccine research. It would appear that an effective vaccine is a definite possibility in the near future, and that in large measure the standards will be based on research carried out by the Division.

An area of current concern and interest to both the Division's and the manufacturers' investigators is that of mycoplasma. Some of these organisms have been incriminated as causes of disease in man. The research currently being conducted on mycoplasmas is of considerable importance since it has been demonstrated that these organisms grow readily in the cell cultures used for producing many virus vaccines.

To accelerate research in this area, an increase of $75,000 is requested by the Division in 1969.

In conclusion, the request of the Division of Biologics Standards for 1969 is $8,499,000 compared with $8,519,000 available in 1968. The net decrease of $20,000 results from the program increase of $75,000 for mycoplasma research and mandatory increases of $80,000, offset by a decrease of $175,000 for nonrecurring equipment costs in 1968.

I shall be happy to respond to any questions you may have.

SUMMARY OF BUDGET REQUEST

Mr. FLOOD. Doctor, there is very little change in the level of your budget. As a result of the application of this famous House joint resolution, the 1968 base is about $8½ million and the estimate for 1969 is for five additional jobs but $20,000 less money. It takes a Scotchman to do that.

Dr. MURRAY. I think this is explained by the fact in the present year there is a certain amount of money of a nonrecurring nature which accounts for the difference.

MYCOPLASMA RESEARCH

Mr. FLOOD. This small staff increase is for a step-up of research in the area of mycoplasma?

Dr. MURRAY. Yes.

Mr. FLOOD. What is that?

Dr. MURRAY. These are complex microorganisms larger than viruses and smaller than bacteria.

Mr. FLOOD. How long have we known them?

Dr. MURRAY. We have known them for 30 years or more in one form or another. A great deal of attention has been focused on them recently because of the implication of their relationship to certain diseases.

Mr. FLOOD. What is the importance of this?

Dr. MURRAY. The importance we are interested in is that mycoplasmas of various kinds occur as contaminants in tissue culture systems used for producing many new virus vaccines. When you are growing cells to produce vaccines these mycoplasmas occur and they have to be identified and excluded from the vaccines. This is true when we are dealing with tissue cultures produced from fertile hens' eggs.

TUMORS CAUSED BY VIRUSES

Mr. FLOOD. On two or three occasions you received increases in your appropriation to work on problems of tumors caused by viruses.

Dr. MURRAY. That is right.

Mr. FLOOD. We read a lot of stories in newspapers and hear a lot on television and radio about diseases caused by viruses.

Dr. MURRAY. One aspect is the so-called possible virus etiology of some forms of cancer.

Mr. FLOOD. That is what people are thinking about, cancer caused by viruses.

Dr. MURRAY. Research in this area is not of primary concern to the division. Our concern is with viruses which may appear as strangers in the course of vaccine production and which can be involved in the production of tumors. We have had that experience with Simian Agent SV–40.

Mr. FLOOD. What do you mean by that?

Dr. MURRAY. It is derived from rhesus monkeys that came from India. On the injection of such materials into hamsters these viruses did produce tumors.

Mr. FLOOD. What is a tumor?

Dr. MURRAY. It is a growth. In these cases it had the characteristics of malignancy.

Mr. FLOOD. This means cancer, I suppose?

Dr. MURRAY. It could be equated with cancer, yes, but there has been no indication this particular virus has any effect in man. Nevertheless, because of our limited knowledge it behooves us to be sure any vaccines we produce are free of such agents.

RH FACTOR

Mr. FLOOD. In this whole broad field are there additional developments or problems you would like to comment on?

Dr. MURRAY. No, except to say that we are concerned with a great many products and these change from time to time and the thrust of our research and also of our control relates to the development of new products or variations of products. One such product that is coming into public interest at the present time is a preparation designed to prevent sensitization of women against the rhesus factor.

Mr. FLOOD. And you are working on that now?

Dr. MURRAY. Yes.

Mr. FLOOD. This is in the area of research?

Dr. MURRAY. Yes, and eventually it will be in the area of control.

ENZYMES

Dr. SHANNON. There is one other area I think the committee should be aware of. This has to do with the fairly rapid development of fractionation of blood and blood products. This is certain to impose a substantial additional burden on the Division, in terms of new problems, and will require a 2-, 3-, or 4-year program. Also enzymes used in human bodies.

Mr. FLOOD. What is an enzyme?

Dr. SHANNON. An enzyme is a complex material that accelerates biological actions. For instance, the enzyme Dr. Mider had in mind is one used to inject into the blood stream to dissolve a clot.

Mr. FLOOD. Mr. Shriver.

RH FACTOR IN BLOOD

Mr. SHRIVER. On page 10 of the justifications there is a brief description of some of the work of your scientists on the Rh factor in blood and the statement is made: "The Division hopes to be able to license $Rh_0$(D) Immune Globulin this year." Would you enlarge on that?

How far along on the study are you and is there a cure for Rh problems?

Dr. MURRAY. We cannot take credit for this kind of work, only for the development of standards in relation to it. It has been demonstrated that an Rh negative woman who has an Rh positive child can be sensitized by the release of some of the red cells from the child into the blood stream of this woman. The child can be normal but the woman may be sensitized so that the next child she has may run into serious problems with Rh disease. The use of serum or plasma, from women who have been highly sensitized, injected into susceptible women within 72 hours after the birth of the child will protect the subsequent children against Rh disease in a large percentage of cases. The use of plasma for this purpose is undesirable for a number of reasons, one of which is the possibility of transmitting a disease such as hepatitis. The preparation that has been developed is a gamma globulin prepared from the blood of highly sensitized women. Experience has shown that gamma globulin does not transmit the virus of hepatitis. This promises to provide a large measure of safety to the recipients.

Mr. SHRIVER. You say you cannot take credit for this?

Dr. MURRAY. No. A great many people have been involved in this. Our role is that such a product must be licensed and we must develop standards to insure its safety and effectiveness.

Mr. SHRIVER. That is all.

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. Doctor, as I understand the amount you are requesting for 1969 is smaller than the amount you requested for 1968. Is that correct?

Dr. MURRAY. That is correct.

Mr. NATCHER. The chairman failed to tell you, Doctor, you are in the right clan.

Mr. FLOOD. Mr. Smith.

Mr. SMITH. With regard to the Rh factor, the paragraph on page 10, you say you cannot take credit for having developed it. Was it developed by Government grantees or under contract or by private industry?

Dr. MURRAY. I cannot say if it was developed by grantees. There have been grantees involved in some of the studies, I know. But I do know the principle here was discovered almost simultaneously on both sides of the Atlantic.

Mr. SMITH. By whom on this side of the Atlantic?

Dr. MURRAY. I would have to give you the names of those.

Mr. SMITH. Was it private industry?

Dr. MURRAY. Some of it was private industry, yes.

QUESTION OF PATENTS ON RH FACTOR PRODUCT AND RUBELLA VACCINE

Mr. SMITH. Who has the patents on it?

Dr. MURRAY. I don't know that there are any patents on it, but it is common knowledge that the firm of Ortho was involved in this and there are others.

Mr. SMITH. Are there patents on it, do you know, Dr. Shannon?

Dr. SHANNON. I suspect that these products make use of conventional fractionation procedures and probably are not patented, but

we will look that up and also look up for you the contribution of our programs to it. I might point out this is something that has been developed over a number of years. There has been serious work in many areas, supported by many people.

Mr. SMITH. Will you look up and furnish the same information with regard to the rubella vaccine?

Dr. SHANNON. Yes.

(The information follows:)

Protection of Rh negative mothers against possible sensitization by the delivery of Rh positive children is based on principles of immunology described as early as 1909 but first applied in the period 1960–62 by several groups of investigators working independently. These were Drs. D. J. Freda, J. G. Gorman, and W. Pollack working at the Columbia University College of Physicians and Surgeons in New York; Drs. R. Finn and C. A. Clarke at the University of Liverpool, England, and Dr. E. G. Hamilton of the St. Louis University School of Medicine. Shortly thereafter, Drs. J. Schneider and O. Priesler at the University of Freiburg, West Germany, conducted similar studies. Both the Freda and Clarke groups received PHS–NIH grant support.

The principles on which this treatment is based are in the public domain, and patents are not applicable.

There have been two major original discoveries in the rubella research program conducted by investigators in the Division of Biologics Standards supported entirely by Division funds. In each instance a patent application has been filed in which the inventors assigned all rights to the Government of the United States. Both discoveries promise to be of considerable public value since they provide the fundamental information necessary for the eventual control of a disease of international consequence.

The first breakthrough was in the discovery of a method by which rubella virus could be attenuated and in the subsequent production and trial of the first safe and effective experimental rubella virus vaccine.

This discovery was reported to the scientific public by Drs. Harry M. Meyer, Jr., and Paul D. Parkman in two papers presented to the annual meeting of the American Pediatric Society in Atlantic City, N.J., on April 27, 1966. More detailed information was published several months later (P. D. Parkman et al, Attenuated Rubella Virus, I. Development and Laboratory Characterization, N. Engl. J. Med. 275:569–574, Sept. 15, 1966, and H. M. Meyer, Jr., et al, Attenuated Rubella Virus, II. Production of an Experimental Live-Virus Vaccine and Clinical Trial, N. Engl. J. Med. 275:575–580, Sept. 15, 1966).

An employee invention report (PHS form 3969) was filed on May 5, 1966, by Drs. Meyer and Parkman and a patent application was filed in their names on December 20, 1966.

The second major achievement concerned the discovery of rubella virus hemagglutination (virus-induced clumping of red blood cells) and the development of a hemagglutination-inhibition (HI) test for the detection of antibodies for rubella virus. This antibody assay procedure is an inexpensive, simple, highly reliable blood test that can be used to determine immunity to rubella. Results are obtained in a matter of hours. Because of these advantages, the new test has essentially replaced all of the earlier methods. It is used for (1) identification of persons immune to rubella (this is particularly useful for women planning families or exposed to rubella); (2) laboratory diagnosis of rubella, and (3) measurement of the immune response induced by experimental rubella vaccines.

This discovery was reported to the scientific public by Dr. Meyer at the annual contractor's meeting of the Vaccine Development Branch of the National Institute of Allergy and Infectious Diseases in Bethesda, Md., on October 6, 1966, and at the annual meeting of the American Academy of Pediatrics in Chicago, Ill., on October 27, 1966. More detailed information was published several months later (G. L. Stewart et al, Rubella-Virus Hemagglutination-Inhibition Test, N. Engl. J. Med. 276: 554–557, Mar. 9, 1967).

An employee invention report was filed by Dr. Harry M. Meyer, Jr., Dr. Paul D. Parkman, Dr. George L. Stewart, Mrs. Hope E. Hopps, Mrs. Barbara C. Meyer, Mr. Robert D. Douglas, and Mrs. Judith P. Hamilton on December 6, 1966, and a patent application was filed in their names on June 26, 1967.

BIOLOGICS STANDARDS INFRACTIONS

Mr. SMITH. On page 7 of your justifications you say the Division's staff is involved, among other things, with the "investigation of infractions of law and regulations and assisting in prosecutions."

How many investigations and prosecutions have you had in the last year?

Dr. MURRAY. I do not believe there have been any actual prosecutions during the past year but there have been a good many investigations of organizations which have not been following the law.

Mr. SMITH. How did you dispose of them?

Dr. MURRAY. We had one in which the U.S. license was summarily suspended in April 1967.

Mr. SMITH. What are the ways of disposing of these cases other than in prosecutions?

Dr. MURRAY. By voluntary compliance in which they agree not to engage in marketing. We do dispose of a few in that way. These are usually minor infractions where people were obviously unsophisticated and not familiar with the law.

Mr. SMITH. How are the bulk of them disposed of?

Dr. MURRAY. Actually there are very few of these cases. We prefer to dispose of them by voluntary compliance. Two of them were disposed of in that way last year, and one involved a blook bank in which this was not possible and the license was revoked.

Mr. SMITH. That is all.

Mr. FLOOD. Mr. Hull.

PRODUCT MONITORING

Mr. HULL. Mr. Chairman, I have only one question.

Dr. Murray, you say once a product has come into use, its safety and potency must be continuously monitored. How do you do that?

Dr. MURRAY. The manufacturer submits copies and summaries of his test results in the form of documents we call protocols.

Mr. HULL. All manufacturers?

Dr. MURRAY. Of this kind of product, yes.

Mr. HULL. How many would be involved?

Dr. MURRAY. There are 218 in toto covering a variety of products. Also, samples of the product are submitted and these are subjected to testing in our laboratories by people who are familiar with the testing procedures.

Mr. HULL. Are these continuing tests?

Dr. MURRAY. Yes. It is only after the product has been shown to satisfy requirements and regulations that a document called a release is issued to the manufacturer. Only then can the product be released in commerce.

Mr. HULL. And do you keep track of it after that?

Dr. MURRAY. Yes.

Mr. HULL. That is all.

Mr. FLOOD. Mr. Laird.

Mr. LAIRD. I think the subject has been adequately covered, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Murray.

Dr. MURRAY. Thank you.

JUSTIFICATION MATERIAL

PUBLIC HEALTH SERVICE

Biologics Standards

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $8,649,000 | $8,499,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| 7 | Biologics standards (Total obligations) | 324 | $8,519,000 | 329 | $8,499,000 | +5 | -$20,000 |
| | Unobligated balance, reserve | 9 | +130,000 | --- | --- | -9 | -130,000 |
| | Total, obligations and reserve | 333 | 8,649,000 | 329 | 8,499,000 | -4 | -150,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 324 | 329 | +5 |
| Full-time equivalent of all other positions..... | 5 | 5 | --- |
| Average number of all employees..... | 283 | 287 | +4 |
| Personnel compensation: | | | |
| Permanent positions..... | $2,353,000 | $2,432,000 | +$79,000 |
| Positions other than permanent..... | 30,000 | 30,000 | --- |
| Other personnel compensation..... | 49,000 | 49,000 | --- |
| Total personnel compensation..... | 2,432,000 | 2,511,000 | +79,000 |
| Personnel benefits..... | 248,000 | 253,000 | +5,000 |
| Travel and transportation of persons..... | 106,000 | 108,000 | +2,000 |
| Transportation of things..... | 10,000 | 10,000 | --- |
| Rent, communications, and utilities..... | 51,000 | 51,000 | --- |
| Printing and reproduction..... | 10,000 | 10,000 | --- |
| Other services..... | 320,000 | 325,000 | +5,000 |
| Project contracts..... | 2,275,000 | 2,275,000 | --- |
| Payment to "National Institutes of Health management fund"..... | 1,845,000 | 1,880,000 | +35,000 |
| Supplies and materials..... | 885,000 | 908,000 | +23,000 |
| Equipment..... | 340,000 | 171,000 | -169,000 |
| Subtotal..... | 8,522,000 | 8,502,000 | -20,000 |
| Quarters and subsistence charges..... | -3,000 | -3,000 | --- |
| Total obligations by object..... | 8,519,000 | 8,499,000 | -20,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $8,649,000 |
| Unobligated balance, reserve | -130,000 |
| 1968 total estimated obligations | 8,519,000 |
| 1969 estimated obligations | 8,499,000 |
| Total change | -20,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of 1968 pay raise costs | --- | --- | --- | $34,000 |
| 2. Extra day of pay in 1969 | --- | --- | --- | 11,000 |
| B. Program | | | | |
| 1. Bacterial products | 21 | $272,000 | 5 | 75,000 |
| Payment to "National Institutes of Health management fund" for centrally furnished services | --- | 1,845,000 | --- | 35,000 |
| Decreases | | | | |
| A. Built-in | | | | |
| 1. Non-recurring items of equipment | --- | --- | --- | -175,000 |
| Total net changes requested | --- | --- | 5 | -20,000 |

Explanation of Changes

Direct operations--The program increase of $75,000 and 5 positions will be used to accelerate research in the area of mycoplasma.

## Biologics Standards

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 324 | $2,677,000 | 329 | $2,761,000 | +5 | +$84,000 |
| Other expenses..... | -- | 5,842,000 | -- | 5,738,000 | -- | -104,000 |
| Total..... | 324 | 8,519,000 | 329 | 8,499,000 | +5 | -20,000 |

### 1968 Program Plans

The Division of Biologics Standards is using the funds available in 1968 to assure the public that the variety of immunizing agents and diagnostic and therapeutic biological products such as vaccines, serums, human blood, its derivatives and similar products are potent, safe and pure for use in human beings. By this is meant that the products are indeed capable of eliciting the bodily reactions that they are purported to do; that they will exercise their prophylactic, diagnostic, or therapeutic effect without inducing undue toxic reactions in the individual to whom they are administered; and that they are free of any unwanted substances.

Current medical practice, both public and private, involves the use of many more vaccines and biologics for preventive measures, particularly in large scale public health programs, than ever before. All indications are that this will continue and expand in the years to come. Thus, (1) the use of these products is more common today than ever before; (2) more people are involved; and (3) the licensing and control of these products is ever growing in importance.

Licensing and control of new and improved products are closely related to scientific and technical developments. New knowledge results in changes in methods of manufacture and new forms of products which require modification or amendment of standards. The Division's staff is involved with developing standards for biologics products, licensing of products and the establishment which produces them; inspection of such licensed establishments to assure the maintenance of high quality in manufacture of products; examination of manufacturer's test results and performance of control tests prior to release; provision of reference standard material for tests; examination of labels and inserts; investigation of infractions of law and regulations and assisting in prosecutions; and promulgation of regulations for new products and amendments of regulations to reflect advances in scientific knowledge and technology. These activities are based on a dual program of control and research.

At the present time, 218 establishments are licensed for the manufacturer of a variety of products. Several of these have subsidiaries. In addition there are 276 blood bank donor centers. There are 1,340 product licenses effective covering 297 licensed products. In terms of workload this means that more than 500 inspections will be made during 1968 and will require approximately 700 man work days. Forty members of the scientific staff will participate in these annual and special inspections to determine that the establishments are complying with standards designed to insure the continued safety, purity and potency of products. Facilities and production methods will be observed and reviewed, records inspected, personnel interviewed, and samples secured from the manufacturers' storage. Samples and test reports of each batch or lot of the products the manufacturer proposes to distribute will be submitted to the Division. Based on past experience, these lots will number between 3,500 and 4,500 and will require approximately 35,000 to 36,000 control tests. In addition, the protocols containing the results of tests performed by the manufacturer will be reviewed for each lot submitted for release.

When necessary, special investigations are conducted to cope with specific situations. In contrast to inspections, investigations concerning possible violations of the Public Health Service Act must be carried out. These call for the expenditure of long and indefinite periods of time in order to obtain all the needed information. Investigations must therefore be carried out by people who have this duty as their main function. At this time, current investigations number approximately fifteen.

As has been pointed out in the past, the Division has few problems of enforcement with the larger producing manufacturers because of the realization that in matters concerning safety and potency of biological products, the public interest is also the interest of the manufacturer. The suspension of a license is a severe penalty and is something an establishment would have great difficulty recovering from economically.

During the course of the year, the Division anticipates filling requests for about 10,000 samples of standard and reference preparations. These preparations will be used to calibrate test procedures and will be used in the evaluation of products. In order to maintain an adequate supply of reference and standard materials it was necessary to prepare 16 antitoxins, 3 serums, 3 vaccines, 2 toxins and 4 skin test antigens during the past year. A total of 478 tests were required to complete satisfactory standardizations of these materials. These tests include such procedures as flocculation reactions, animal protection tests, animal titrations, neutralizations and assorted _in vivo_ (animal) and _in vitro_ (test tube) tests on specific specialized materials.

The Division's contract research program, which complements its in-house research, covers a wide spectrum. Problems of viral oncogenesis (tumors caused by viruses) constitute the major focus of the program. This program involves testing of viral and other vaccines for oncogenic potentiality in animals, studies designed to reveal the presence of covert or otherwise undetectable

agents in cell culture and in other production systems used in the manufacture of human viral vaccines, studies on normal human karyotypes to provide information on human diploid cell culture systems, and other projects. Studies of the safety of mineral oil and emulsifiers, and of oil-adjuvant vaccines, are being performed on a number of contracts, and additional contract effort is devoted to the related subject of the toxicology and oncogenic potentiality of various chemically defined substances used as inactivants, preservatives and stabilizers in vaccines. Additional contracts have or are being negotiated on studies encompassing mycoplasmas, effects of plastic constituents on blood, attenuated measles vaccine, poison ivy, yellow fever, poison oak, latent virus and many more.

While direct research is also being conducted on most facets covered by research contracts, basically, the Division's research is product-oriented and therefore concerned with all biological products subject to license; some of these are new and some are older products which require updating. Only in this way is the Division able to develop the most meaningful and useful standards for the products produced under license.

The research relates to all aspects of manufacture, distribution, and use and effects of biological products, on the biological phenomena involved in immunization, in allergies and desensitization, and in the fractionation, aging, and degradation of blood and blood products. Research is in progress on a large variety of bacterial and fungal products, viral and rickettsial vaccines, allergens, blood and blood derivatives, antitoxins, and antivenins. The Division is also concerned with research on the containers in which products are stored or dispensed. It is engaged in research on adjuvants, which are added to vaccines to enhance their protective effect, on stabilizers, and on chemical and physical methods of inactivating infectious agents.

Division scientists have been conducting laboratory and clinical studies with an attenuated mumps virus vaccine which recently become commercially available. The primary goal was in test development and in evaluating the safety and efficacy of the experimental vaccine for man. These studies confirmed and extended the data obtained by the manufacturer. Consequently, this year, standards have been established governing the manufacture and release for general use of attenuated mumps vaccine.

This is an important step forward for the public as this "childhood" disease can be very serious for adults, especially males, since often it results in sterility.

The attenuated rubella virus strain, reported last year, has received world wide distribution for experimental investigation. Work with this virus is continuing to encourage U.S. research workers and the international scientific community to feel that rubella control is a realistic goal of the near future.

An experimental live rubella virus vaccine produced by the Division has been subject to additional clinical trials by the Division's scientists as

well as other groups here and abroad. More than 500 persons have thus far been successfully immunized with the experimental material under conditions of clinical investigation. None has manifested any signs of rash or other clinical reaction, thus indicating that the virus is attenuated.

A most promising endeavor by the Division's scientists is a study on the Rh factor in blood which causes sensitization of certain women. Working with manufacturers on new test methods, the Division hopes to be able to license $Rh_o(D)$ Immune Globulin this year. This form of gamma globulin will be used in the prevention of "Rh disease" (erythroblastosis fetalis).

Division personnel have completed their moves into the new facilities and the shake-down period, although not without problems, is approaching an end. Renovations in building 29 are presently being accomplished and it is expected that before the year is through the space involved will be operational.

Program Plans for 1969

It is envisioned that the Division's programs will continue as outlined for 1968 and will adapt themselves to the needs posed by further scientific advances and manufacturing problems.

In 1969, the Division is requesting a program increase of five positions and $75,000 to concentrate on the area of mycoplasma. (Mycoplasma is an organism which is intermediate between bacteria and viruses in size). Division scientists have been working with mycoplasma on a limited basis. The increase would be used to accelerate this effort. The known and suspected roles of mycoplasmas in human disease makes it necessary to assure that vaccines be free of these organisms. Mycoplasma organisms grow readily in the cell culture systems used for producing many new virus vaccines. Their exclusion from the vaccines can be achieved only by use of elaborate test procedures. Measles and poliovirus vaccines are tested routinely. These tests are also being extended to experimental vaccines now in course of evaluation. Development of new test procedures and the testing of vaccines as they are produced will require a greater expenditure of time and effort on the part of the Division.

Included in this budget request are $11,000 for an additional day's pay in 1969 and $34,000 for annualization of pay raises, as well as $35,000 increase in the NIH management fund for centrally provided services. These increases, in addition to the program increase of $75,000 are offset by $175,000 in non-recurring funds for equipment. This results in a net decrease of $20,000.

MONDAY, MARCH 18, 1968.

# NATIONAL CANCER INSTITUTE

## WITNESSES

DR. KENNETH M. ENDICOTT, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
ROBERT E. LEARMOUTH, EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE
DR. JESSE L. STEINFELD, ASSOCIATE DIRECTOR FOR PROGRAM, NATIONAL CANCER INSTITUTE
EARLE L. BROWNING, BUDGET OFFICER, NATIONAL CANCER INSTITUTE
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| PUBLIC HEALTH SERVICE | | | |
| Personnel compensation: | | | |
| Permanent positions | 12,116 | 13,277 | 13,901 |
| Positions other than permanent | 183 | 162 | 163 |
| Other personnel compensation | 113 | 114 | 114 |
| Total personnel compensation | 12,412 | 13,553 | 14,178 |
| Personnel benefits | 1,311 | 1,589 | 1,640 |
| Travel and transportation of persons | 626 | 626 | 726 |
| Transportation of things | 106 | 106 | 106 |
| Rent, communications, and utilities | 422 | 422 | 422 |
| Printing and reproduction | 353 | 404 | 404 |
| Other services | 1,079 | 1,287 | 1,487 |
| Project contracts | 46,665 | 50,777 | 51,843 |
| Payments to "National Institutes of Health management fund" | 8,836 | 9,607 | 9,708 |
| Supplies and materials | 2,883 | 2,991 | 3,350 |
| Equipment | 2,656 | 2,000 | 2,000 |
| Grants, subsidies, and contributions | 92,067 | 97,332 | 100,815 |
| Subtotal | 169,416 | 180,694 | 186,679 |
| Quarters and subsistence charges | −10 | −10 | −10 |
| Total obligations, Public Health Service | 169,406 | 180,684 | 186,669 |
| ALLOCATION TO VETERANS' ADMINISTRATION | | | |
| Personnel compensation: | | | |
| Permanent positions | 601 | 596 | 602 |
| Positions other than permanent | 148 | 155 | 156 |
| Other personnel compensation | 1 | 1 | 1 |
| Total personnel compensation | 750 | 752 | 759 |
| Personnel benefits | 54 | 54 | 55 |
| Travel and transportation of persons | 73 | 71 | 71 |
| Transportation of things | 1 | 1 | 1 |
| Rent, communications, and utilities | 1 | 1 | 1 |
| Other services | 26 | 30 | 30 |
| Supplies and materials | 40 | 54 | 54 |
| Equipment | 57 | 67 | 67 |
| Total obligations, Veterans' Administration | 1,002 | 1,030 | 1,038 |
| Total obligations | 170,408 | 181,714 | 187,707 |

PERSONNEL SUMMARY

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| **PUBLIC HEALTH SERVICE** | | | |
| Total number of permanent positions | 1,421 | 1,419 | 1,462 |
| Full time equivalent of other positions | 35 | 30 | 30 |
| Average number of all employees | 1,364 | 1,432 | 1,460 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |
| **ALLOCATION TO VETERANS' ADMINISTRATION** | | | |
| Total number of permanent positions | 82 | 82 | 82 |
| Full time equivalent of other positions | 9 | 10 | 10 |
| Average number of all employees | 94 | 86 | 86 |
| Average GS grade | 5.3 | 5.3 | 5.3 |
| Average GS salary | $6,253 | $6,547 | $6,547 |
| Average salary of ungraded positions | $14,116 | $14,780 | $14,780 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | | | |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 76,881 | 81,656 | 84,752 |
| (b) Fellowships | 3,171 | 4,326 | 4,422 |
| (c) Training | 12,015 | 11,350 | 11,641 |
| Total grants | 92,067 | 97,332 | 100,815 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 14,372 | 16,032 | 16,533 |
| (b) Collaborative research and development | 60,433 | 63,077 | 65,111 |
| (c) Biometry, epidemiology, and field studies | 1,329 | 1,415 | 1,435 |
| (d) Review and approval of grants | 2,351 | 2,542 | 2,520 |
| (e) Program direction | 1,143 | 1,316 | 1,293 |
| Total direct operations | 79,628 | 84,382 | 86,892 |
| Total program costs, funded [1] | 171,695 | 181,714 | 187,707 |
| Change in selected resources [2] | −1,287 | | |
| Total obligations | 170,408 | 181,714 | 187,707 |
| Financing: | | | |
| Comparative transfers to other accounts | 2,875 | | |
| Unobligated balance lapsing | 2,361 | 1,642 | |
| New obligational authority | 175,644 | 183,356 | 187,707 |
| New obligational authority: | | | |
| Appropriation | 175,656 | 183,356 | 187,707 |
| Transferred to other accounts | −12 | | |
| Appropriation (adjusted) | 175,644 | 183,356 | 187,707 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 170,408 | 181,714 | 187,707 |
| Receipts and other offsets (items 11 to 17) | 2,875 | | |
| Obligations affecting expenditures | 173,283 | 181,714 | 187,707 |
| Obligated balance, start of year | 106,230 | 121,557 | 138,297 |
| Obligated balance, end of year | −121,557 | −138,297 | −161,004 |
| Adjustments in expired accounts | −3,354 | | |
| Expenditures | 154,604 | 164,974 | 165,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 71,908 | 76,713 | 76,000 |
| Out of prior authorizations | 82,696 | 88,261 | 89,000 |

[1] Includes capital outlay as follows: 1967, $1,473,000; 1968, $2,067,000; 1969, $2,067,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders. 1966, $50,019,000; 1967, $48,762,000; 1968, $48,762,000; 1969, $48,762,000.

Mr. FLOOD. Now we have the National Cancer Institute of the Public Health Service and the presentation will be made by Dr. Kenneth M. Endicott, the Director.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

I see we have a biographical sketch of you, Dr. Endicott, which we will insert in the record.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH

Name: Kenneth Milo Endicott, M.D.

Position: Assistant Surgeon General, Public Health Service, Director, National Cancer Institute.

Birthplace and date: Canon City, Colo.; June 6, 1916.

Education: A.B., University of Colorado, Boulder, 1936; M.D., University of Colorado, Denver, 1939.

Experience: Director, National Cancer Institute, National Institutes of Health, U.S. Public Health Service, Department of Health, Education, and Welfare, July 1960– ; appointed Assistant Surgeon General, U.S. Public Health Service, January 1960; Associate Director, National Institutes of Health, 1958–60; Chief, Cancer Chemotherapy National Service Center, National Cancer Institute, 1955–58; Scientific Director, Division of Research Grants, National Institutes of Health, 1951–55; Chief, Section on Metabolic and Degenerative Diseases, Division of Pathology, National Institutes of Health, 1942–51; Medical Center for Federal Prisoners, Springfield, Mo., 1942; Maritime Quarantine Station, San Francisco, Calif., 1941–42; U.S. Public Health Service Relief and Quarantine Station, Portland, Oreg., 1940; commissioned in U.S. Public Health Service, 1939.

Association memberships: Diplomate, American Board of Pathology; American Medical Association, fellow; American Association for the Advancement of Science; American Association of Pathologists and Bacteriologists; Society for Experimental Biology; International Association of Medical Museums; Society for Experimental Pathology; Washington Academy of Sciences; Alpha Omega Alpha; Phi Rho Sigma; Theta Xi.

Special awards, citations, or publications: Distinguished Service Medal of the Public Health Service Commissioned Corps, awarded 1964: "For his outstanding and distinguished leadership in Medical Research Administration and National Cancer Research Programs."

GENERAL STATEMENT

Mr. FLOOD. Please proceed, Dr. Endicott.

Dr. ENDICOTT. Mr. Chairman, and members of the committee, research and related activities in program areas of the National Cancer Institute that offer substantial promise of progress in prevention and treatment will be augmented to the greatest extent possible in the coming fiscal year.

DETECTION OF UTERINE CANCER

Important progress already made against several forms of human cancer has been encouraging. Early detection and prompt treatment have reduced deaths from uterine cancer 40 percent in the last 25 years.

Mr. FLOOD. How often should a female after the age of puberty be examined and when should she start, at age 12, 13, 14? How often should she have it done and when should she stop, with or without children, married or unmarried?

Dr. ENDICOTT. There is a considerable difference of opinion. I do not think anybody really knows what the ideal frequency is.

Mr. FLOOD. What would you advise your wife?

Dr. ENDICOTT. She is in the age group where I see to it that she has a Pap smear at least once a year.

Mr. FLOOD. What is a Pap smear?

Dr. ENDICOTT. It is an examination of a uterine cervical smear for cancer cells.

DETECTION OF BREAST CANCER

Mr. FLOOD. Is there a test for cancer of the breast?

Dr. ENDICOTT. There are two in addition simply to a physical examination. I consider them to be still in the experimental stage. One is called mammography and it is actually taking X-ray pictures of the breast. The other is called thermography.

Mr. FLOOD. How often should it be done?

Dr. ENDICOTT. In terms of incidence—to go back to the Pap test, the incidence in teenagers is so low that it probably would not be worthwhile.

Mr. FLOOD. Do you have daughters?

Dr. ENDICOTT. Yes, sir; I have daughters.

Mr. FLOOD. How old is your youngest daughter?

Dr. ENDICOTT. Fourteen.

Mr. FLOOD. What do you tell her?

Dr. ENDICOTT. I would not suggest she have a test.

Mr. FLOOD. But my wife should have one how often?

Dr. ENDICOTT. She should have an annual physical examination, and that should be a part of the annual physical examination.

Mr. FLOOD. Is this expensive?

Dr. ENDICOTT. Not very. It costs about $5.

In mammography we have a test going on at the health insurance plan of New York.

Mr. FLOOD. What is mammography?

Dr. ENDICOTT. X-ray photography of the breast to detect it before you can feel it.

Mr. FLOOD. Is that expensive?

Dr. ENDICOTT. It is more expensive.

Mr. FLOOD. Can that be done in a doctor's office?

Dr. ENDICOTT. The smear can be taken in the doctor's office and it can be sent anywhere for examination.

Mr. FLOOD. You can go to your family doctor and he can do this?

Dr. ENDICOTT. That is right.

Mr. FLOOD. Suppose he has a nurse, can a nurse do it or must it be a doctor? Can a technician take a smear?

Dr. ENDICOTT. I think you could train a nurse or a technician to do this adequately in a matter of a week or so. The technique is not difficult. Mammography is a different story. It requires special X-ray equipment and that would not be generally found in a doctor's office.

Mr. FLOOD. But for a Pap test your family physician can do it and under certain circumstances a good technician can do it and it is not expensive?

Dr. ENDICOTT. That is correct.

Mr. FLOOD. On mammography this is different?

Dr. ENDICOTT. The cost for a set of films is about $25 or $50. It does require special equipment and special training on the part of the

radiologist to interpret the X-ray. So I do not regard this as ready for general application.

Mr. FLOOD. When would you advise your daughter to start her annual tests, the Pap test and mammography? Before she is married?

Dr. ENDICOTT. I think a good time to begin is when she is married, if she is married in her twenties, let us say. The risk from cervical cancer increases materially with childbearing.

Mr. FLOOD. Why?

Dr. ENDICOTT. It is probably related to the trauma to the uterus in childbearing.

HODGKIN'S DISEASE

Dr. ENDICOTT. Long-term remissions, amounting virtually to cure, have been produced in 40 percent of early Hodgkin's disease patients treated with X-ray.

Mr. FLOOD. What is Hodgkin's disease?

Dr. ENDICOTT. It involves the lymph nodes and the spleen.

Mr. FLOOD. Is this a type of cancer?

Dr. ENDICOTT. Yes.

Mr. FLOOD. We are led to believe it is incurable.

Dr. ENDICOTT. It has been regarded as incurable but there are a number of patients in some series of studies who have not had a recurrence of the disease after 10 or 15 years.

Mr. FLOOD. In describing Hodgkin's disease you pointed to your neck and throat.

Dr. ENDICOTT. Of course, lymph nodes are in the neck. They are usually the first involved in Hodgkin's disease. When you see a person with a lump on both sides of his throat you immediately think that Hodgkin's disease must not be ruled out.

Mr. FLOOD. Male and female?

Dr. ENDICOTT. Male and female.

Mr. FLOOD. Can it be cured?

Dr. ENDICOTT. There are a number of patients now who are between 10 and 15 years after treatment without a recurrence of the disease. I think they almost have to be regarded as cures.

Mr. FLOOD. Is there an age problem?

Dr. ENDICOTT. Well, it is usually not seen in children. It is seen in young adults and then there is another large cluster of cases that begin in age groups 55 to 65, but they are probably two different diseases, because one affects young adults and the other affects people in advanced middle age. It affects both sexes.

LEUKEMIA

Survival of children with acute leukemia has been increased from weeks or months to years with drug treatment.

Mr. FLOOD. Are there different kinds of leukemia?

Dr. ENDICOTT. Yes, they now identify six different varieties of acute and chronic leukemia. The most common in children is acute leukemia; then there is what is known as lymphatic leukemia.

Mr. FLOOD. We have heard if you have leukemia as an adult it is fatal. Does that mean what it says.

Dr. ENDICOTT. It means what it says and it is also fatal if you have

it as a child. The thing is, though, I believe, as in the case with Hodgkin's disease, we now have a small number of children who have probably been cured because, here again, we have quite an impressive number of children who have lived 5 years and a few who have lived 10 years without the disease after completion of treatment. In the untreated, the fulminating nature of the disease is such that I, myself, am convinced they are cures.

Mr. FLOOD. We have known men who have been strong all their lives into their late fifties and all of a sudden they become ill and they go to the hospital and then you hear they have leukemia. Here is a strong, virile man, an athlete. He goes to the hospital on Sunday and they say he has leukemia and he is dead in $x$ months. Why is that?

Dr. ENDICOTT. I can think of two possible reasons. First of all, sometimes acute leukemia, although it is normally a disease of children, occurs in adults.

Mr. FLOOD. What is leukemia?

Dr. ENDICOTT. It is a form of cancer in which cells are produced out of control, the white cells of the blood. Normal white cells of the blood are in effect displaced by these abnormal nonfunctioning leukemia cells.

Mr. FLOOD. This man has had a physical examination every year for 40 years. Why wouldn't it be found?

Dr. ENDICOTT. One reason might be because it was not there?

In acute leukemia, the onset is very rapid, it may go from the appearance of the first symptom to death in a matter of a few weeks.

Mr. FLOOD. Is this an abnormal cell division process?

Dr. ENDICOTT. The cells divide just like normal cells would divide, but they do it more often and they never stop. They are multiplying abnormally.

Mr. FLOOD. I was thinking of a colleague of ours who was a very vigorous fellow, very famous intercollegiate athlete. All of a sudden he became ill and 2 or 3 days later somebody said he had leukemia. He lived a short time and died.

This is a nasty business. You know when it comes close to the family or friends, it is quite a shock. What are you doing about this?

Dr. ENDICOTT. We have a very, very intensive program in leukemia, both from the standpoint of treatment and from the standpoint of prevention, and here I believe we will in the end prove that leukemia is a virus disease. I am satisfied that some day we will be able to prevent it with a vaccine. We have a very, very aggressive program, large and active program in leukemia.

We have a special report on this program which I would be happy to place in the record.

(The report follows:)

SPECIAL REPORT:
ACUTE LEUKEMIA

Patients with acute leukemia currently being treated at major research centers in the United States have a vastly better outlook for survival than did patients 20 years ago. Recent analysis of studies initiated just a few years ago reveals the remarkable pace at which gains are being made. Progress was sharply defined at a recent Symposium on Clinical Aspects of Acute Leukemia and Burkitt's Tumor co-sponsored by the National Cancer Institute and the American Cancer Society in Boston. The meeting, held September 20, 1967, honored the 20th anniversary of Dr. Sidney Farber's clinical usage of the first effective anti-leukemia agent, aminopterin.

Dr. C. Gordon Zubrod, Scientific Director for Chemotherapy, National Cancer Institute, reported to the meeting that the percentage of patients with acute lymphocytic leukemia achieving complete remission, or disappearance of all evidence of disease, had risen from about 50 percent reported in 1964, to greater than 90 percent at present. In 1964 the median survival time of these patients ranged from 12 to 19 months. According to Dr. Zubrod, the median survival time of such patients now starting treatment at major research centers may be between 4 and 5 years. The percentage of complete remissions being achieved in acute granulocytic leukemia has also risen sharply; this may foreshadow prolongation of survival for patients with this more difficult-to-treat type of acute leukemia.

Also at the Boston meeting, Dr. Joseph Burchenal of the Sloan-Kettering Institute for Cancer Research presented a report on the Long-Term Survival Registry of the Acute Leukemia Task Force. The registry now lists 157 patients with acute leukemia who survived 5 years or more after diagnosis of their disease. The cases were located by means of a survey in which questionnaires were mailed to hematologists all over the world. Thirty of the 157 long-term survivors have been adults, and 127 children. Of the 30 adults, 16 were reported to be alive with no evidence of disease. Of the 127 children, 87 were reported alive and without evidence of disease.

Dr. Burchenal reported that a discontinuance of therapy appears justifiable and perhaps advisable 7 years from diagnosis of the disease if the patient has had no evidence of disease for at least 4 years. Forty-eight of the 103 patients without evidence of disease have been

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Prepared January 1968 by the National Cancer Institute, Public Health Service, U. S. Department of Health, Education, and Welfare in connection with 1969 appropriation hearings.

without treatment for a year or more. Ten of the patients have been without treatment for 10 years or more.

Anti-leukemia drugs used in combination continue to be the most promising approach to treatment. Prednisone, vincristine, mercaptopurine and methotrexate are most often used, but other drugs are also effective. With the recent advent of several promising materials it is quite possible that even better treatment combinations for the acute leukemias will be found.

In April 1964 a 4-drug treatment developed by NCI scientists, Drs. Emil J. Freireich, Myron Karon and Emil Frei, III, was reported to the American Association for Cancer Research. Sixteen children were included in this study. Their median survival time after diagnosis was about two years. As of January 1968, two of the children are surviving, one 4½ years and the other 5 years after diagnosis.

Other combination chemotherapy schedules were subsequently devised. In June 1967, Dr. Edward S. Henderson, Head of the Leukemia Service, National Cancer Institute, reported to the International Congress of Chemotherapy in Vienna on his continuing study of 35 patients with acute lymphocytic leukemia treated with 4 drugs given in massive doses on an intermittent schedule. As of January 1968, median survival time of the 35 children is estimated to be about 3 years following the start of the treatment. Attempted correlations of the patients' remission periods with estimated cell division rates of leukemic cells suggest that this 4-drug schedule may eliminate a patient's pool of rapidly dividing leukemic cells and relapses may be due to cell growth by a second pool of more slowly growing cells.

During 1967 the roles of several relatively new anti-leukemia drugs were explored by scientists at the National Cancer Institute and several NCI-supported research centers. Cytosine arabinoside, a pyrimidine analog that inhibits DNA synthesis, was studied at the Institute and at grantee institutions including the Sloan-Kettering Institute for Cancer Research and cooperative medical centers of the Children's Cancer Study Group A. Cytosine arabinoside was found effective in inducing remissions in acute granulocytic leukemia, acute lymphocytic leukemia refractory to other drugs, and acute undifferentiated leukemia of childhood. Reports on the research were presented at a meeting of the American Association for Cancer Research in April 1967.

Daunomycin and an apparently identical antibiotic from France, rubidomycin, have also proven useful in both the lymphocytic and

granulocytic forms of acute leukemia. Studies of the drugs have been conducted by NCI's two cooperative leukemia study groups, the Children's Cancer Study Group A and Acute Leukemia Cooperative Group B. Clinicians at the Hopital St. Louis in Paris, a member of Group B, have had extensive experience with rubidomycin and have achieved complete remissions of acute granulocytic leukemia in 51 percent of patients treated.

Combination therapy using the new drugs is being studied. Clinicians at NCI-supported Sloan-Kettering Institute reported inducing remissions by the use of daunomycin in combination with prednisone. Cytosine arabinoside is also being used in combination therapy.

Newer agents such as bis chloroethyl nitroso urea (BCNU), L-asparaginase, and 6 methyl mercaptopurine riboside (6-MMPR) are also under evaluation for effectiveness in acute leukemia. L-asparaginase, an enzyme found in animal tissues and bacteria, was widely publicized during 1967. Although many years may elapse before its true usefulness is known, it appears to have activity against acute lymphocytic leukemias that require asparagine for growth. The National Cancer Institute is supporting research on L-asparaginase at 10 grantee institutions and has contract arrangements with a leading drug manufacturer for purification and production of the material in sufficient quantity to permit an adequate clinical trial. Approximately 50 patients with leukemia or related forms of cancer will be treated with L-asparaginase during 1968 at the National Cancer Institute and its grantee institution, the Memorial Sloan-Kettering Cancer Center in New York City.

SUPPORTIVE THERAPY

Allopurinol, a drug developed by Drs. Gertrude Elion and George Hitchings of the Burroughs-Wellcome Company, has recently earned a place in the therapy of acute leukemia patients. Until recently, patients were often seriously threatened by kidney damage resulting from the administration of anti-leukemia drugs. (These drugs break down leukemic cells, releasing uric acid into the bloodstream; in large amounts, uric acid crystallizes and forms kidney stones.) Allopurinol, by blocking the formation of uric acid, alleviates the threat of kidney failure among these patients.

Transfusions of blood platelets, small disc-shaped particles essential to the blood clotting mechanism, continue to be an essential part of therapy at centers equipped to provide intensive drug treatment to leukemia patients. As of December 1967, there were 28 medical centers participating in the NCI's platelet transfusion program, supported by a total of $1,265,765 in PHS grants during 1967.

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The role of platelets in preventing life-threatening hemorrhages among leukemia patients is now firmly established. At the National Cancer Institute patients whose platelet level has fallen to dangerous lows may receive 6 to 8 units of platelets per day.

In an effort to assure a readily available supply of stored blood platelets, the National Cancer Institute has continued to support research into freeze-preservation techniques. An important step toward this goal during 1967 was the successful manufacture of platelet storage bags designed according to the recommendations of the Acute Leukemia Task Force for freeze-preservation procedures. Preliminary studies of frozen platelets suggest that they have about half the efficacy of fresh platelets, hence twice as many may be needed to prevent hemorrhage.

It is infection, not hemorrhage, that is now the leading cause of death among patients with acute leukemia. Gram-negative bacteria, which are often resistant to treatment with antibiotics, are the most serious source of infection. To counter these infections, the National Cancer Institute has taken several approaches.

A major one is NCI's development of a blood cell separator to make available to patients adequate yields of granulocytes, the white blood cells that are effective in fighting infections. In 2 hours the separator can process the entire blood supply of a normal donor or a patient with an abundance of white cells, remove the granulocytes and return the other blood elements to the donor in a continuous-flow procedure. The instrument was developed during the past several years under contract arrangements with International Business Machines Corporation. During 1967 it was used for the first time at the Clinical Center, NIH, in continuous-flow operation as a source of granulocytes to minimize the danger of infection to patients with acute leukemia.

Donating granulocytes in this manner is not hazardous to the blood donor since never more than a pint of his blood is outside his body at a given time. Moreover, granulocyte loss is not a problem to the donor since the normal individual has fifty to one hundred times as many white blood cells elsewhere in his body, e.g. the bone marrow, as are present in the peripheral blood.

Another means of countering infection is hospitalization of patients in an atmosphere as nearly germfree as possible. During 1967, the National Cancer Institute advanced such research through the support of "Life Islands" at 5 centers--The Clinical Center of NIH, the M. D. Anderson Hospital and Tumor Institute in Houston, Roswell Park Memorial Institute in Buffalo, Maimonides Hospital in Brooklyn, and Mt. Sinai

As of December 1, 1967 the leukemia surveillance program included 10 reporting areas: the States of Connecticut, Rhode Island, Utah and Washington, and the metropolitan areas of Alameda County, California; Atlanta, Georgia; Kansas City, Kansas and Missouri; Minneapolis-St. Paul, Minnesota; Harris County, Texas; and Nassau County, New York. Data are obtained on a continuing basis through State and local health departments. Information received from July 1966 through June 1967 showed a total of 583 cases in the first 8 reporting areas mentioned above, somewhat fewer than might be expected from 1960 incidence estimates. However, a lag in the reporting of chronic cases and the national decline in leukemia mortality reported by Drs. Fraumeni and Miller may explain the lower figure.

THE OUTLOOK

The discoveries and advances made in the late 1940's and 1950's in the treatment of leukemia patients at the major research centers were mirrored only dimly in the early 1960's at the average hospital in the United States. Dr. Sidney J. Cutler and his associates in the End Results Section of the National Cancer Institute published a report in the November 1967 issue of the Journal of the National Cancer Institute, "Ten Thousand Cases of Leukemia: 1940-62." The report concerns patients treated in 98 hospitals of various types and sizes, all but 16 having no university affiliation. The data reveal that from 1940 to 1962 increasing use of chemotherapy improved the survival time of patients, particularly children with the lymphocytic form of acute leukemia. However, despite the improvement in survival among these children, the outlook in 1962 for the average patient at the average hospital was poor.

How the new treatment regimens introduced more recently at major research centers will affect the survival experience of the average patient with leukemia remains to be seen. NCI's End Results Section will continue to collect data and report its findings.

All leukemia patients will not, however, have equal prospects for long-term survival until the complex treatments now available at major research centers become generally available. This will require major scientific, educational and technologic efforts by not only Government and major research institutions but also private hospitals and local physicians.

Techniques of patient care now being developed at research centers will have to be adapted for use at smaller hospitals. One such technique, the administration of platelet transfusions to reduce the risk of hemorrhage, may soon be more widely available, thanks to the NCI-sponsored production of frozen platelets which can be shipped by air throughout the United States.

The National Cancer Institute, through its research and improved communications systems, is working hard to speed the day when each leukemia patient will be provided with nothing less than the most effective therapy available.

Hospital in New York City. The "Life Island," a plastic isolator that encloses a patient's bed in a bubble of virtually germfree air, is being evaluated at the National Cancer Institute.

Because of psychologic problems that may confront many patients within the limited confines of the "Life Island," NCI is also continuing to support the development of room size areas for germfree treatment, so-called "laminar flow rooms" where the patient is protected from infection by a controlled flow of recirculating, filtered air. Visitors entering downwind from the patient cannot infect him with bacteria because the contaminated air is blown into filters and rendered germfree before it is recirculated to the patient. Laminar flow treatment areas are being evaluated at NIH and at a NCI contract-supported unit at the University of Minnesota.

An even newer concept would employ a portable laminar flow unit such as the one the National Cancer Institute is attempting to develop. Such a portable unit would transform an ordinary hospital room into a "protective environment" for virtually germfree care, without the extensive building modifications required to install a laminar flow room.

To make the benefits of intensive therapy and supportive care available to as many patients as possible, the National Cancer Institute has continued its domiciliary care program whereby a leukemia patient and his guardian may travel to a major treatment center and be housed nearby during out-patient periods. Domiciliary care funds in the amount of $117,462 were made available for patients through NCI grants to 18 centers during 1967.

LEUKEMIA INCIDENCE AND MORTALITY

For the first time a decrease in leukemia mortality rates has been observed in the United States. NCI scientists Drs. Joseph F. Fraumeni, Jr. and Robert W. Miller reported in the March 3, 1967 issue of Science that the most recent 5-year period studied (1961-65) showed lower leukemia death rates for the white population than all previous periods. (The pattern was less clear among non-whites because of their smaller numbers.) Although the decline occurred among all age groups from 1 through 74 years, the decrease was greatest among children aged 1 to 4. Possible explanations include a more conservative use of X-ray among children by physicians, following widely publicized reports in 1956 on hazardous effects of excessive radiation. Some scientists also believe that the longer survival of leukemia patients treated chemotherapeutically may also play a role in the downturn.

Of continuing interest to scientists at the National Cancer Institute are reports of "clusters" of cases of leukemia, although at present it appears that such clusters can be attributed only to chance. Since 1966 the National Cancer Institute has been cooperating with the National Communicable Disease Center in a leukemia surveillance program to develop accurate data on leukemia incidence in the United States and to identify individual cases or groups of cases of particular interest in terms of various environmental, genetic and virologic factors.

INCREASE IN CANCER DEATH RATE

Dr. ENDICOTT (proceeding with his prepared statement). But despite steady improvement in the cure rate, the cancer death rate continues to creep up year by year.

Mr. FLOOD. Is that because of the increase in population?

Dr. ENDICOTT. That is part of it, of course.

Part of it is aging of the population. But there is a net increase which one just has to assume is due to new causes of cancer. Most of us think that the principal factor is chemical contamination of environment.

Mr. FLOOD. You were about to tell me this is caused by a virus, and sooner or later, you will have a vaccine to attack cancer.

You have come a long way in 20 years.

Dr. ENDICOTT. In at least some form. As a matter of fact, I think we have come a long way in 5 years in this area or even in the past year. The work is moving very fast. To me it is by far and away the most exciting part of the whole field of cancer.

There will be a total of 600,000 new cases this year and 315,000 deaths. There will be 61,000 new cases of lung cancer and 55,000 deaths, mostly of men. Breast cancer will take the lives of 28,000 women. Cancer of the colon and rectum will kill 45,000 of both sexes.

CANCER OF LOWER BOWEL

Mr. FLOOD. This cancer of the lower bowel is peculiar to males?

Dr. ENDICOTT. No, sir; it is not, but it is more common in men than in women.

Mr. FLOOD. What will produce cancer of the lower bowel?

Dr. ENDICOTT. We really do not know, sir. It is certainly true that the large bowel and especially the lower end of the large bowel is more susceptible to cancer than the small bowel. Why this should be we can only speculate. We do not really know what causes cancer of the large bowel.

Of course, the best presumption is that it is some material in the bowl content in the partially digested food and the residues of the food and digestive juices in the inside of the bowel.

Mr. FLOOD. Is it a common cancer?

Dr. ENDICOTT. Yes, sir. It causes 45,000 deaths a year. The leading single cause of cancer deaths is lung cancer, 55,000, so 45,000 would rank about second.

As I say, we do not really know what the cause of it is. It may be viral, too, I do not know.

Dr. SHANNON. I think one thing that might want some clarification here is that the upper end of the gastrointestinal tract and the lower end of the gastrointestinal tract represent quite different environments?

Mr. FLOOD. What divides them?

Dr. SHANNON. The upper gastrointestinal tract is that part above the colon and the lower is the colon and rectum.

The upper tract has the mouth and esophagus and stomach. All three of these areas are quite susceptible to cancer, the smaller intestinal tract is essentially the duodenum, the jejunum and the ileum.

The colon and rectum are highly susceptible to cancer. The upper part of the gastrointestinal tract is the food intake and the chemical intake. It is affected by other things but these are the dominant ones. In the middle or lower part of the upper gastrointestinal tract there is, in general, no high concentration of any material. This is why there is an exchange across the membrane without any high degree of——

Mr. FLOOD. Does the mastication of food affect it?

Dr. SHANNON. I do not believe so. In the lower end of the gastrointestinal tract there is a striking absorption of water and, therefore, a high concentration of the residual contents of the gastrointestinal material. It is a totally different environment than the middle.

Mr. FLOOD. It is the end of the line and you have all the trouble there?

Dr. SHANNON. Anything there will be highly concentrated because of the absorption of water. So you have a broad variation of environments in the gastrointestinal tract. So there is a physiological base for there being a high degree of difference in the susceptibility of its parts to cancer.

### CANCER OF THE STOMACH

Dr. ENDICOTT. Just as an aside, one of the most puzzling things at the present time is the steady decrease in the incidence of cancer of the stomach in the United States. We do not know why this is happening, and I wish I did. We might learn something from it to make other kinds of cancer decrease. But stomach cancer in the United States is going steadily downward.

Mr. FLOOD. You found this out about what year? What is the timetable on this?

Dr. ENDICOTT. The trend became noticeable in the early fifties and picked up quite rapidly. I recall we were starting a series of studies on the treatment of cancer of the stomach and we arranged with a certain number of hospitals to carry out these studies.

Mr. FLOOD. How do you treat cancer of the stomach?

Dr. ENDICOTT. By surgical removal of the stomach——

Mr. FLOOD. I did not have that in mind.

Dr. ENDICOTT. What we were trying, sir, was to see if we could not improve the cure rate, which is poor.

Mr. FLOOD. Is this surgery the last thing you do?

Dr. ENDICOTT. No, sir; it is the only thing you can do. And the cure rate is only about 5 percent. And we had hoped that by using drugs at the time of surgery we might kill the cancer cells that the surgeon's knife did not find to reduce the number of recurrences. Recurrence is very common.

Mr. FLOOD. Is there a sex problem here in the cancer of the stomach?

Dr. ENDICOTT. It is more common in men.

Mr. FLOOD. Why?

Dr. ENDICOTT. I do not know.

We need to make deep inroads into specific cancer problems by well-planned approaches.

LUNG CANCER

Two new task forces—the Lung Cancer Task Force established at the direction of the President, and the Breast Cancer Task Force established by the National Cancer Institute—will be allocated funds to develop their programs.

Lung cancer is responsible for more deaths than any other form of cancer. The cure rate is still only about 5 percent. Smoking is recognized, of course, as the principal cause of lung cancer. Research into the development of a less hazardous cigarette has therefore been given high priority by the Lung Cancer Task Force.

Occupational and atmospheric exposures are also being investigated as causes of lung cancer. This requires many sophisticated resources, including fully defined analytic testing and screening systems and skilled people to establish and operate them. As another approach, it may be possible to modify the biologic makeup of the individual in a fashion that would reduce his susceptibility to lung cancer. This is a highly speculative possibility but one that should not be overlooked.

If all this work should be started today and should succeed, many people would still fall victim to lung cancer before the situation could be very much improved because of the exposure which they have already had. To cope with the lung cancer situation in which we are living, we need much better methods of detecting and diagnosing the disease, and much more effective methods of treating it; as we know, a few cases are cured by surgery. I think perhaps the best-known case is that of Arthur Godfrey who is 5, 6, 7 years past surgery for lung cancer.

Improved outlook for the patient under treatment has always been a major goal of the National Cancer Institute.

Mr. FLOOD. You say surgery for cancer produces a very minimal saving of life.

Dr. ENDICOTT. In the case of cancer of the lungs and cancer of the stomach, the cure rate is awfully low. It is on the order of 5 percent. In cancer of the breast—as well as many others—the batting average is very much better.

Mr. FLOOD. Is this the removal of the entire breast?

Dr. ENDICOTT. Yes, sir; radical removal of the breast.

Mr. FLOOD. If a cancer takes place in the right breast and then is removed, could there be a recurrence in the left breast of the same cancer?

Dr. ENDICOTT. Could be, because there are vascular connections which cross midline and this sometimes happens. Presumably that woman has some kind of susceptibility or she would not have gotten the first one, and the risk of her getting a new cancer in the other breast is substantially greater than in the normal woman.

Mr. FLOOD. Is cancer of the breast more common than we think?

Dr. ENDICOTT. No, sir. I think that this is one form of the disease which is seldom missed, the diagnosis may be made somewhat late, but I doubt that there are very many cases of cancer of the breast that are unrecognized.

SKIN CANCER

Mr. FLOOD. Is there a high incidence of skin cancers through exposure to the sun?

Dr. ENDICOTT. It is more common in some areas of the world than others. In the United States there is a relatively very high incidence of skin cancer.

Mr. FLOOD. Does the pigmentation of the skin control this or affect it in any way?

Dr. ENDICOTT. Yes, sir; quite definitely.

There are certain complexions that are much more susceptible to skin cancer than others. Cancer of the skin is quite rare in the Negro or in the person with a brunette complexion. It tends to occur in the blond, the redhead, the sandy-haired Scotsman type.

Mr. FLOOD. It is a question of pigmentation then?

Dr. ENDICOTT. It is a question of pigmentation to a very considerable extent.

Mr. FLOOD. This is not uncommon?

Dr. ENDICOTT. No; it is very common. Here the cure rate is on the order of 95 percent, which is pretty good. It can be effectively cured with surgery, with radiation or with drugs. And of course the most important thing is it is on the outside where you can see it and detect it early.

Mr. FLOOD. Go ahead.

CANCER CENTERS

Dr. ENDICOTT. That goal has been approached best in institutions where teams of specialists combine their resources and skills for accurate diagnoisis and effective therapy. Some 20 institutions of this kind that have been receiving grant support are situated mainly in the northeastern region of the country.

Mr. FLOOD. Why?

Dr. ENDICOTT. Because there has been enough interest either on the part of a State government or of a municipality or a wealthy philanthropist to create them, and that is where most of them are located, from here to Boston. There are a couple of exceptions.

One of the world's great cancer centers, for example, is in Houston, Tex., the M. D. Anderson Hospital. That one was created by the State; it is supported by the State government. There is in effect another cancer center at the University of Wisconsin. We are attempting to do something about this, very actively encouraging institutions in parts of the country that do not have cancer centers to establish them, and I think we are beginning to make real progress and that 5 or 10 years from now you will see a greatly altered situation with a number of new centers in the South, the Middle West, and Far West.

HEART, CANCER, AND STROKE PROGRAM

Mr. FLOOD. To what extent has your shop participated in the recent heart, cancer, and stroke program—in the setting up of regional centers on heart, cancer, and stroke—with particular reference to the cancer part?

Dr. ENDICOTT. We have worked very closely with them, sir. As you know, that program at the moment is still largely in the planning stage. There are very few operational grants that have been made.

Mr. FLOOD. Will you help me get the one in Pennsylvania, based on Philadelphia, off the ground?

Dr. ENDICOTT. On that one we will need help. They have the same problem as all of the big metropolitan areas who are having a terrible time getting this thing off the ground. But for the most part these regions are still planning.

What we are trying to do, sir, is to help the institutions which are going to be at the center of a region to develop the cancer part of their program by providing those forms of support that would appropriately come from the Cancer Institute. I hope we can stay a jump or two ahead of them, so that there will be something in terms of an excellent clinical cancer program in the center which is serving the region.

Mr. FLOOD. Is this development covered all through the 50 States on the heart, cancer, and stroke program? Are they being organized?

Dr. ENDICOTT. I think I am correct—Dr. Shannon could correct me in this—I believe all of the country is now covered.

Mr. FLOOD. They are planning.

Dr. ENDICOTT. In the planning stage. But in terms of operations, it really is still not off the ground. I am disturbed about one thing, Mr. Chairman. I am deeply disturbed about the lack of attention to cancer problems, at least in the planning stages of many of these proposals, and if we cannot pep them up somehow that part of it is not going to amount to much.

Mr. FLOOD. What is it, all heart?

Dr. ENDICOTT. It is mostly cardiovascular.

Dr. SHANNON. Mr. Chairman, this again reflects, as Dr. Endicott pointed out, that over the past 30 years there has arisen in the Northeastern United States a large number of highly sophisticated research centers. He mentioned Wisconsin and Houston, Tex., as being outside the Northeast part of the country but, other than that, there are very few sophisticated environments. When a practical problem, such as the heart, cancer, stroke problems, comes along, which requires the modification of the delivery system to improve the techniques for the diagnosis and treatment of the diseases, it cannot go beyond the level of sophistication in the region.

Now in the cancer area, the lack of a high degree of sophistication, particularly the lack of a highly integrated cancer program, is serving as a barrier for the development of the cancer aspects of this program. This is why Dr. Endicott says that he hopes that he can keep ahead of the development of the regional medical programs so that they can look forward to having the regional competence upon which to base the more practically applied delivery system.

I think this is a very good example of the lack of sophistication imposing a ceiling on what can be done.

Mr. FLOOD. It strikes me as being odd a universally known killer like cancer would be receiving so little attention in this program where it was meant to be certainly equal to the cardiovascular program. I wonder why?

Dr. SHANNON. I can answer that.

The treatment of cancer has been largely based on our surgery groups and surgery specialists. Until recent years, they have not acquired, except in a few places, the high degree of sophistication that is necessary for mounting sound investigative programs. In general, you will find that the use of more complex procedures, whether they

be diagnostic or therapeutic, depends, first, upon development of investigative capabilities which then influence the individuals who are provding personal health services.

What is happening now, and I think Dr. Endicott would agree, is that people other than surgeons have a reawakened interest in the cancer problem. You have people in a wide variety of disciplines entering the field from the scientific standpoint and this will provide the science base for the application of new knowledge. But this is a developing thing rather than one that has already developed.

### CANCER CENTERS

Dr. ENDICOTT (proceeding with his prepared statement). It is proposed to make a grant of sufficient funds in fiscal 1969 to establish another in an area not now served by such a facility.

It is our hope, in fact, that in time a sufficient number of cancer centers equipped and staffed to conduct research and training, and make the best medical and hospital care available to cancer patients in the areas they serve, will be established wherever needed. Some may be incorporated into the regional medical programs now under development under Federal legislative authorization. In any case, the ideal center will be essentially a functional unit having a relationship to a medical educational institution, a specific goal of attacking problems in human cancer, and a multidisciplinary and interdisciplinary approach to research and treatment.

The center concept is an inevitable development in the plan of total attack on the cancer problem envisioned when the National Cancer Institute Act was adopted 31 years ago. It is a logical step toward the ultimate objective we seek: total control of cancer. It is the concept of thorough integration of research, education and medical practice for the most sophisticated approach to the management of disease that modern medical science can devise. It will give patients the benefit of diagnosis and treatment employing the individual or combined skills of specialists in every related field. It will constantly improve the education and training of the medical students and young doctors who become a part of a center's operating complex. And it will stimulate continued fundamental research and hasten the application of new knowledge and techniques to the management of human cancer.

There is no doubt that the ultimate solution to the mystery of cancer will be found through fundamental research on the cancerous process and the tumor-host relationship. These studies underlie all the progress that has been made against cancer, and will be continued and expanded through both the intramural and extramural programs of the Institute. A program increase in research grants not only will allow the establishment of an additional cancer research center as previously mentioned, but will also support continued research in cancer causation, tumor growth, host-tumor relationship, epidemiology, diagnosis, and therapy. Grants will also be provided for the continuation of ongoing programs of graduate and clinical training.

### SUMMARY OF BUDGET REQUEST

Mr. Chairman, the request for the National Cancer Institute for 1969 is $187,707,000, compared to the 1968 operating level of $181,714,000. The 1969 budget contains increases of $5,993,000 including:

$3,096,000 for research grants; $96,000 for research fellowships; $291,000 for training grants; and $2,510,000 for direct operations.

I shall be happy to respond to any questions you may have.

Mr. FLOOD. Doctor, I have a few questions to ask.

After House Joint Resolution 888, your budget for 1968 totaled $181,714,000. You are asking for $187,707,000, an increase of $5,993,000.

Dr. ENDICOTT. Yes, sir.

RESEARCH GRANT SUPPORT FOR 1969

Mr. FLOOD. That is very little more than 3 percent. More than half of this is for research grants. But on page 28 of your justification you said you will not be able to support quite as many in the 1969 budget as you are supporting this year.

What is the matter, are too few good proposals being submitted? Are they not coming up with ideas?

Dr. ENDICOTT. No, sir. We are not being able to support all of the approved good proposals. At the present time we are able to support about two-thirds of the approved competing proposals. By that I mean the new ones or the continuations that have run out of commitment and have to come up and be reviewed and compete again. So we are supporting about two-thirds of them and the price of doing research, the cost per grant, is going up.

There is another factor in this: We are making a concerted effort to consolidate a number of small projects into a smaller number of larger projects. So that in part this reflects an increase in costs and in part it reflects some packaging, some conscious packaging of efforts on our part.

APPLICATIONS BACKLOG

Mr. FLOOD. What about your backlog of applications?

What did you have in backlog at the end of 1967, and what do you forecast for 1968 and 1969?

Dr. ENDICOTT. I can supply that for the record, but it was on the order of $5 million last year. It will be about that much again this year.

(The information follows:)

BACKLOG OF GRANT APPLICATIONS

The backlog of grant applications is provided in the following table. This includes unfinanced approvals for regular research grants, specialized research centers, training, and fellowship grants:

| | 1967 | | 1968 | | 1969 | |
|---|---|---|---|---|---|---|
| | Number | Amount | Number | Amount | Number | Amount |
| Total unfinanced approvals | 208 | $6,269,000 | 180 | $7,641,000 | 164 | $10,089,000 |

SPECIALIZED RESEARCH CENTERS

Mr. FLOOD. You talked about specialized research centers, but you did not tell us where they were. Suppose you supply for the record where these specialized centers are located.

(The information follows:)

*Location of specialized research centers*

| *State* | *Institution* |
|---|---|
| California | Stanford University. |
| Connecticut | Yale University. |
| Louisiana | Tulane University. |
| Maryland | University of Maryland. |
| Do | Johns Hopkins University. |
| Massachusetts | Childrens Cancer Research Foundation, Inc. |
| Do | Beth Israel Hospital. |
| Michigan | Michigan Cancer Foundation, Inc. |
| Minnesota | University of Minnesota. |
| Missouri | Cancer Research Center. |
| Do | Washington University. |
| New York | Memorial Sloan-Kettering Cancer Center. |
| Do | Health Research, Inc. |
| Ohio | Case Western Reserve University. |
| Oklahoma | Oklahoma Medical Research Foundation. |
| Pennsylvania | Institute for Cancer Research. |
| Do | Allegheny General Hospital. |
| Do | Temple University. |
| Tennessee | St. Jude Childrens Research Hospital. |
| Texas | M. D. Anderson Hospital. |
| Washington | University of Washington. |
| Wisconsin | University of Wisconsin. |

Mr. FLOOD. Now tell us why you need an additional $720,000?

Dr. ENDICOTT. It will permit us to start one new one. They cost more than that to run when they are fully operated. But that is a reasonable startup cost.

Mr. FLOOD. How many do you have?

Dr. ENDICOTT. Depending on how you define it, there are 20 to 25. Most of them are quite incomplete. The number of really complete cancer centers is substantially less than that. I would say fully developed cancer centers, there are probably no more than five in the United States.

FELLOWSHIPS AND TRAINING GRANTS

Mr. FLOOD. You have an increase of $96,000 for fellowships and an increase of $291,000 for training grants, but that is not enough to support as many grants as you are supporting this year.

Dr. ENDICOTT. That is true.

Mr. FLOOD. Does that mean these increases you are asking for are not enough to cover the mandatory cost increases?

Dr. ENDICOTT. In the fellowships, of course, we set the stipend. The costs in the training grants are not directly controllable by us. It reflects, I think, an upward trend in salaries and stipends in universities performing training in various parts of the country.

DIRECT RESEARCH

Mr. FLOOD. You have an increase here from $16,032,000 to $16,533,000 for laboratory and clinical research. It provides a very small increase in program activities. This is your direct research program using Federal employees. Why this increase when you are cutting back in the number of grants?

Dr. ENDICOTT. The increases which we have asked here really represent a little less than what is necessary to maintain the existing program. We will be cutting back actually in the number of people being trained, but the costs have gone up.

Mr. FLOOD. But you are adding Federal jobs.

CANCER TASK FORCES

Dr. ENDICOTT. We are asking for an increase in positions to mount a lung cancer task force, and a few in our own laboratories but those are the only federal jobs I am talking about. The increase for our own laboratories is even less than in grants.

Mr. FLOOD. You have a real increase for the task force.

Dr. ENDICOTT. Yes, sir.

Mr. FLOOD. You will recall that the first of these so-called task forces was started by congressional appropriation, as a matter of fact, by this subcommittee a few years ago.

Dr. ENDICOTT. Yes, sir, the breast cancer task force.

Mr. FLOOD. What developments have you to report so far? What do you intend to do if and when you get this increase for 1969?

Dr. ENDICOTT. We are approaching it from several standpoints. First of all, treatment. This is one form of cancer which does respond to some extent to drugs. So we are intensifying our study of drugs as an added weapon in the control of the disease, and beginning to make some real progress by combining drugs with surgery. If you give drugs at the same time you operate, the cancers recur less frequently. So that is one area of the approach.

Another thing we are doing, we have already mentioned today, and that is mammography, the use of X–ray as a way to find the tumors earlier.

ADVANCES IN CANCER THERAPY

Mr. FLOOD. Have you any advances to report since you were before the committee last year in cancer therapy?

Dr. ENDICOTT. Yes, sir. There has been a very exciting new development, and this is the discovery that you can bring about remissions in acute leukemia by the use of an enzyme. This is a material which should not be particularly toxic, whereas all of the other drugs that we use in acute leukemia are intensely toxic. And it is too early yet to say what this will mean, but there can be no question that about half of the patients with acute lymphatic leukemia will go into complete remission if this particular enzyme is injected into their blood.

Mr. FLOOD. Is there anything to this talk about a vaccine against cancer?

Dr. ENDICOTT. Yes, sir. There is a lot to it, but not in man yet. It is perfectly feasible to protect experimental animals.

SWEDISH GRANTEE

Mr. FLOOD. Would you tell us about that Swedish grantee who went on television with his vaccine. There was some criticism of you for supporting that work in its earlier stages.

Dr. ENDICOTT. That was a bad investment. The application was to support work carried on in animals. The work he had been doing up to that time in animals was very highly regarded. What the man did I believe was to attempt to go into man without having carried out enough work in the laboratory to be justified in giving this material to human volunteers. He not only gave it to human volunteers against advice, but in order to encourage volunteers to get into the program—these were elderly people on some kind of an insurance program—he went on television and shot himself with a substance on TV.

Mr. FLOOD. Will you supply for the record the name of this person and a little bit more about the program, how you got into it and how you got out of it?

Dr. ENDICOTT. Yes, sir; I will be happy to do that.

Mr. FLOOD. Mr. Natcher?

Mr. NATCHER. Doctor, in submitting the other information our chairman has requested, I wonder if you would also place in the record the amount of the grant or grants.

Dr. ENDICOTT. Yes, sir.

Mr. NATCHER. Thank you, Mr. Chairman.

(The information follows:)

RESEARCH PROGRAM IN SWEDEN

Because of the important contributions he had made in the field of cancer immunology, Dr. Knut Bertil Bjorklund of the State Bacteriology Laboratory in Stockholm, Sweden, was invited to submit a research grant application as part of the cancer virology program being developed by the National Cancer Institute in 1958. Dr. Bjorklund submitted an application which was reviewed by study section and the National Advisory Cancer Council and was recommended for approval for 5 years with a very high priority.

The research project was a laboratory study concerned with identification of antigenic substances derived from cancer cells growing in tissue culture and preparation of antibodies to these antigens by injecting the antigens into experimental animals; the antibodies so produced were to be studied for their effect on cancer cells growing in tissue culture. The grant was awarded with a 5-year period of commitment, and the first 3 years were paid as follows:

| | |
|---|---|
| C 4587 (R1) 1959 | $41,249 |
| C 4587 (C1) 1960 | 38,300 |
| C 4587 (C2) 1961 | 58,000 |
| Total awarded | 137,549 |

During the course of the third year Dr. Bjorklund, against the advice of prominent Swedish health officials, prepared a vaccine from human cancer cells and initiated a program of vaccinating normal human volunteers. In order to promote this project Dr. Bjorklund appeared on Swedish television and inoculated himself with the vaccine to demonstrate his confidence in its safety. The scientific and medical community in Sweden publicly censured Dr. Bjorklund, and the whole matter became a public concern with the press, the Government, and the universities all involved in the controversy.

Upon making inquiry, the National Cancer Institute learned that although the preparation and testing of the human vaccine had not been a part of the grant application, grant funds had in fact been used to defray part of the cost of the vaccine preparation. It was also discovered that although the Immunological Research Laboratory to which the grant was made was housed in the State

Bacteriology Laboratory (which in Sweden is roughly the equivalent of our Division of Biologics Standards which has regulatory powers over biologic products such as vaccines), the Immunological Research Laboratory was administratively independent and had no appropriate organizational apparatus for the review of research involving human beings. The National Cancer Institute, therefore, notified Dr. Bjorklund that no further support would be given unless the application was submitted on his behalf by an institution which had adequate organization for the review and control of human experimentation. No such application was ever filed, and the National Cancer Institute support terminated at that point.

As a result of this and several similar experiences in which grantees utilized grant funds to support studies in man which were not disclosed in the grant application, the Public Health Service established policy and regulation which require grantee institutions to file their institutional polices and procedures for regulating human studies for approval by the Public Health Service and to give assurances that these policies and procedures will be enforced for all research support to that institution from the Public Health Service.

CHEMOTHERAPY RESEARCH

Mr. FLOOD. I was going to also ask about your chemotherapy program but I have already taken considerable time and other members have questions, however, I do want to place your special report on this subject in the record.

(The report referred to follows:)

SPECIAL REPORT:
CHEMOTHERAPY RESEARCH

The concern of the National Cancer Institute in drug development derives from the continuing increase in cancer morbidity and mortality despite classic treatment. Systemically administered drugs represent the only present means to improve upon the results of surgery and X-ray. That the concern and investment in drug control has been worthwhile is clear, since the effort at NCI, starting in 1946 and greatly expanded in 1955 has led to the apparent cures of several types of cancer by means of drugs; and those successes in turn, to a knowledge of basic principles of chemical control that promise to extend to a number of the common tumors.

The activities of the NCI in chemical control of cancer date from the formation of a section of chemotherapy in 1946. This evolved by 1951 into the Laboratory of Chemical Pharmacology. In 1953 the Clinical Center opened and clinical studies were begun by the Medicine Branch and by the Endocrinology Branch. Experimental and clinical pharmacology grew and both gradually focused on the clinical pharmacology of antitumor drugs. In 1963 these intramural activities were merged under an Associate Scientific Director in charge of Clinical and Experimental Therapeutics. In 1965 all activities of NCI in drug research were consolidated under a Scientific Director for Chemotherapy.

In 1955, the Congress asked NCI to undertake a large scale attempt to find new and better antitumor drugs. At that time the work throughout the country was highly fragmented and can be grouped as follows:

1 - Considerable fundamental research on the biology and biochemistry of animal tumors, supported both by grants in universities and directly in the laboratories of NCI at Bethesda;

2 - Small and unpopular clinical studies in a few university hospitals;

3 - A few small drug development programs (i.e. an entire program from screening of drugs through clinical trial) in cancer research institutes such as the Children's Cancer Research Foundation under Dr. Sidney Farber; the Sloan-Kettering Institute under the late Dr. Cornelius P. Rhoads; and the NCI operation under Dr. C. Gordon Zubrod.

These drug development programs contained both internal components and external but loose arrangements with the pharmaceutical industry and

university laboratories, neither of which had much spontaneous interest in antitumor drug development.

The Cooperative Program, 1955-65. In 1955, the authorization and money for a broader program, permitted the beginnings of a full scale effort in research and development of antitumor drugs. This could not be accomplished through coordination of existing resources, since most of the elements of a drug development program did not exist. In the years 1955-65, NCI, under the leadership of Dr. Kenneth M. Endicott and later Drs. Stuart M. Sessoms, Robert D. Coghill, T. Phillip Waalkes and Joseph D. Leiter, used these new resources to develop all the requisite building blocks--sources of new drugs from chemists and from natural products, animal tumor systems for the screening of the chemicals, rigorous animal studies for the toxicity and safety of new drugs, resources for the study of how the new drugs behaved in animals and man, the formulation of the drug into a product safe and appropriate for use in patients and finally, the clinical trial itself.

The process of developing these resources required most of the 10 years and the expenditure of $250 million. The reasons for this are clear-cut. There was so little known about how to approach the problem, that each of these resources had to be created almost in its entirety. Worse than this, in each area there were many possible options and there was no consensus in the scientific community as to where to begin. This meant that the major options (i.e. lines of possibly rewarding research) had to be created and then compared and finally a choice made as to which option to select.

For example, in the screening of drugs for antitumor activity in animals, there were several hundred animal tumors that could be used. Each of these had its special (scientific) pleader. It was decided to study a half dozen of the best systems. But before this could be done on a large enough scale to make a comparison, animal production had to be built up to obtain enough animals to run the tests. Major problems arose on the genetic and disease control of animals, bred on such a large scale. When these problems had been sorted out, corrected and comparisons of drugs made, the major question was still unanswered--how well did these animal test systems predict for activity in human tumors?

Though animal studies (once the problems above have been attended to) can be completed in six months to a year, cancer in patients is slow-paced. While this may not seem so to the patient with uncontrolled cancer, the evolution of most cancers takes two to five years. This implies that when an investigator gets a new drug or concept, proves in animals that it is worthwhile, and safe to study in man, he can reach a judgment

of efficacy no sooner than two years after he completes the study. The clinical study itself will require between one and two years. Hence even after the investigator has finished the animal work, the earliest he can see what a drug does in clinical cancer is four years, and the average is well above five years.

While the problems of animal testing were being sorted out, the National Cancer Institute in 1955 initiated a careful study of clinical trials for antitumor drugs. There were many unanswered problems--what kinds of patients should be studied; what drugs should be used; how many patients in a trial; how long to give the drugs; what kinds of trials were morally and ethically defensible; how should such trials be reviewed and supported--etc., etc. Many avenues were pursued in order to find the answers since no one had a ready solution. Over the 10 years there developed a cadre of physicians who became skilled in such clinical studies. On the clinical side then, the period 1955-65 was a time of training that led to a small but key resource--a clinical apparatus at last able to tackle the major question--Do the animal tumor studies predict what will happen to clinical cancer?

The Reorganized and Enlarged Program. In 1964 the Wooldridge Committee raised some concerns about the magnitude of the cancer chemotherapy effort and cited the program unfavorably. The NCI in 1965 asked four of its staff to examine the 10 years of effort and recommend action. This was done and a report made. As a result of this analysis and recommendation, Dr. Zubrod in September 1965 was asked to assume responsibility for the chemotherapy program and to implement the recommendations. The major objective was to create a strong management group that could use the tools created during 1955-65. It was possible because of the analysis, to identify all the key steps for more rapid drug development, and to use the existing framework for a highly coordinated operation in consumating the critical steps. In order to bring this about, all activities concerning drug development of NCI were grouped under the chemotherapy program. These included the laboratory and clinical research at Bethesda, contracts for working with industry and (a portion of the) grants for carrying out clinical research in the universities. This permitted the growth of a closely knit scientific organization in many ways akin to a large pharmaceutical house, yet going far beyond industrial capacity to carry out clinical investigations. The program also made extensive use of small working groups, such as Task Forces, wherein scientists, physicians, contractors and grantees analyzed their results and hammered out better ways of accomplishing given tasks. This led to the growth of strong management capabilities in the top scientific and medical staff, with an opportunity for close surveillance of NCI's own research, the

performance of contractors and the contributions of the grantees. By close surveillance in no way does any interference with the day to day operations of scientists and physicians, but the ever-present question in the minds of the top staff, as they considered results and planned the use of resources, "How does this contribute to the chemical control of cancer?" This question could be precisely framed by management because of the existence as previously mentioned of a detailed overall plan of the critical steps to successful chemical control of cancer.

The results obtained in the last two years from this coordinated use of resources, have led to a new capacity for drug control of the rapidly growing tumors, and to a substantial clue as to what must be done to achieve similar control of slower growing tumors. Because of these rapid advances the chemotherapy area is in the midst of a second major analysis of critical steps to success, as modified by the new information. And again it will be possible to reexamine the total apparatus and ask how each piece contributes to the functioning of the new plan.

Current Objectives and Accomplishments. The chemotherapy program as it now operates has two general objectives:

1 - To identify in the more than three million known chemical compounds, those chemicals that will best control cancer. As one corollary, of course, there is the objective to find chemical compounds now unknown but existing in nature--in bacteria, plants, and animals. A second corollary is to find out enough about the antitumor activity of the known effective drugs in animals and man, that it becomes possible to relate chemical structure with the desired antitumor activity. This growing knowledge will then enable the chemist to custom tailor new drugs to produce the desired effect.

One result of the analysis of the 1955-65 experience was a decision to change the primary animal tumor system screen. It now consists of L1210 leukemia in the mouse and Walker 256 in the rat. The new primary screen requires only one-third as much material as the old one and, for strongly positive compounds, permits much earlier decisions. It achieves a thousand-fold concentration of most of the probable active compounds and permits rapid pursuit of highly active chemicals.

A new modality is assuming increasing importance in the decision to go for full clinical trial of selected compounds, namely the demonstration by the methods of Skipper and of Bruce, of exploitable selective toxicity for the tumor. This has stimulated an extraordinary amount of research on selective toxicity, and conceptual and technical advances are occurring rapidly. Quantitative systems permit discrimination among

the myriad of agents, dosage schedules, and drug combinations, in favor of high selectivity for tumor cell kill. These promising leads are now under test in the clinic.

Experience has underlined the importance of enriching the mix entering the primary screen. Random sampling of the chemical universe cannot be abandoned, because it continues to enjoy more success than directed sampling in the selection of key compounds from among both synthetics and natural products. It has recently led to the discovery of important structures such as the nitrosoureas and the tetracycline glycosides. While random sampling must continue, especially in areas previously neglected, there is at hand a sufficient number of chemicals that cause regression of clinical cancer, to undertake a study of the relation of chemical structure to (antitumor) function. A group of top organic chemists has been meeting with NCI staff for careful study of these problems. The results have shown that the choice of synthetic compounds for introduction into the screen will progressively be determined by structure-function considerations, so that directed synthesis will gradually displace random screening. Although many compounds active against tumors are appearing from natural products, the establishment of structure is so rapid that these randomly-determined new structures soon add their contributions to the total structure-function mosaic.

2 - To study the best ways in which to use the effective drugs in man. This is a more fundamental scientific problem than might appear from the simple phrase, and actually goes right to the nature of the cancer cell--why it is that a cancer cell multiplies without regard to the rules of the body. The sensitivity of cancers to drugs is somehow related to the rate at which they grow. As mentioned above, chemical control has advanced remarkably for the rapidly growing tumors--choriocarcinoma, the acute leukemias, Hodgkin's disease, Wilms's tumor, etc. It seems likely that application of present knowledge will bring about almost complete control of these diseases. (Rate of application is dependent on education of the medical profession, and availability of dollars and other resources of a magnitude not at hand.) As this sensitivity to drugs has been studied on a fundamental level, it has been discovered that the biologic situation (especially the fraction of tumor cells dividing at any one time) in the slow growing tumors is entirely different from the more rapidly growing tumors. The new knowledge has been put into a variety of animal model systems, and the lessons of these models are in study in man--and the answer of success or failure is five plus years away.

Increasing experience with the correlations between drug effects in animals and man leads to stronger confidence in the ability of animal

studies to predict safe dosage and possible side effects in patients, except as regards the central nervous system. Man's extraordinary capacity for abstraction and subtle motor activities would seem to dampen the chances that drug-induced behavioral defects in man will be anticipated by gross changes in the dog or monkey. Each time such a discrepancy occurs, the offending drug is reexamined intensively in animals, with perhaps some slight enlightenment.

A highly rewarding effort has been through comparative studies of pharmacological disposition. Comparative pharmacology has been neglected for antitumor drugs. The chemotherapy program has been intensified in its efforts to ensure thorough pharmacologic study of each of the active drugs. One of the first rewards followed examination of cyclophosphamide. This drug is a superb antitumor agent in experimental animal systems. While it is perhaps the best of the alkylating agents in clinical cancer, its performance falls short of the animal model. It has been shown by Mellett of Southern Research Institute that the effective metabolite of cyclophosphamide is present in high concentration in the mouse and the rat, but in low concentrations in patients. Identification of the active moiety and its direct administration to patients is the next step.

In the rapidly growing tumors there have been substantial advances. Clinical cancer has been shown to be responsive to several new drugs, namely, Daunomycin, dibromomannitol and 6-methylmercaptopurine riboside. Secondly, animal systems have successfully predicted more effective dosage schedules for cytosine arabinoside. Thirdly, drug combinations have been used to improve considerably both percentage remissions and survival times in several of the hemotologic neoplasms.

For the slow growing (solid) tumors there is increasing realization that changes in tumor size following chemotherapy cannot occur rapidly and that drug administration must be undertaken at the time of surgical excision and continued for a year or more, if tumor regression is to be observed. Such studies are in progress for cancer of the colon and cancer of the lung.

A special opportunity exists for improvement in the treatment of acute myelocytic leukemia and of Hodgkin's disease. Acute myelocytic leukemia has not yielded to chemotherapy in the same manner as the lymphocytic variety. Four new treatments have appeared, namely, (1) better utilization of combinations of known drugs, (2) 50 percent complete remission by Daunomycin, (3) 50 percent complete remission by 6-methylmercaptopurine plus 6-mercaptopurine, and (4) 60 percent complete remission by a more effective drug schedule of cytosine

arabinoside. The full coordination of these new therapies may well add substantially to the survival of patients with acute myelocytic leukemia. Similarly, the use of drug combinations in far advanced Hodgkin's disease has produced a high percentage of complete remissions. The utilization of adequate radiation therapy and adequate chemotherapy certainly increases the cure rate for Hodgkin's disease.

Similar opportunities are emerging in other areas, as the experimental models show the way with improved drugs, dosage schedules and combinations. The clinical proofs of improved chemical control come forth slowly, as cancer is a slow-paced disease, and end points of effective drug therapy are never spectacular. A highly efficient clinical trials apparatus is essential if these opportunities are to be seized.

The Assessment. In looking back at the situation of 1955, it is apparent that there were a number of small fragments of research and development with the general goal of chemical control of cancer. The vigorous 10 year effort from 1955-65, by the NCI, has led to the creation of the proper resources for a full scale program of drug development. The emergence of a strong scientific management group since 1965 has allowed the coordination of these resources toward a single goal with the successive steps clearly defined. The effect upon the pharmaceutical industry has been to encourage them to make available to this scientific team a great variety of compounds, and to search out or synthesize new materials. More importantly, pharmaceutical and other biomedical industry has been encouraged to help the scientific team under contract for a host of skills not available in universities or government--these include such functions as difficult chemical synthesis, large scale production and purification, breeding of large numbers of animals, extensive toxicology studies required by FDA regulations, quality control of drug manufacture and formulation of drugs for human use. It seems highly unlikely that a single pharmaceutical house will undertake antitumor drug development. In the first place industry generally reserves such major research and development programs for diseases that afflict several millions of Americans. The likelihood is that each type of cancer will turn out to be a separate disease, and that any given drug will be useful to less than 100,000 patients at any one time. Secondly, the major problems of the biology of cancer must be answered in the clinic, and the pharmaceutical industry has virtually no capacity to get involved in the highly complex problem of clinical investigation of cancer. If there is to be a vigorous program for drug development in cancer this must be done by the Federal Government. This is in keeping with one of the major functions of the National Institutes of Health as stated by Dr. Shannon: "The programs of the NIH are directed toward the accomplishment of... (11) Research programs, national in character, centrally organized and directed, with specific and definable goals. The degree to which a substantial amount of fundamental, though relevant, research is contained in these programs will depend upon the area of study, the state of knowledge, and the particular goals selected."

Mr. FLOOD. Mr. Laird?

Mr. LAIRD. Dr. Endicott, we have before us your justification on the increases in personnel and in the grant programs. This increase for the grant program provides for a level of funding comparable to this year's level; is that correct?

Dr. ENDICOTT. Yes, it is, approximately.

Mr. LAIRD. In the exchange you had here a few minutes ago, there was some indication that the number of grants would be at a lower level; is that correct?

Dr. ENDICOTT. Yes; slightly lower.

Mr. LAIRD. But the total amount of dollars will be slightly higher; is that not correct?

Dr. ENDICOTT. That is correct.

### EFFECT OF BUDGETARY CUTBACK

Mr. LAIRD. If a percentage freeze is placed upon this budget—I understand there may be such an announcement made shortly—what would be the effect of that freeze and where would it be applied in the National Cancer Institute? I understand 10 percent has been under discussion.

Dr. ENDICOTT. I would have to make some calculations and it would be difficult to do this just in my head. But I am pretty sure we would have to stop making new grants and probably would not be able to fund too very many of the continuation grants that came up to compete. I do not think that a 10-percent cut would make it necessary for us to fail to honor our commitments, but we might have to try to negotiate the commitments down. I would have to calculate just what this means.

Mr. LAIRD. What would it do to your traineeship program and your personnel program?

Dr. ENDICOTT. A lot would depend, of course, on whether one could select where to take this cut or whether it was just 10 percent of every item here.

Mr. LAIRD. If it is in the form of an expenditure limitation, you would be able to apply the limitation to the lower priority items, would you not?

Dr. ENDICOTT. I would hope so. Some expenditures are easier to cut off in a hurry than others. Obviously if you stop making new grants you are not cutting off something that is an ongoing program. If scientists know they are coming up for competition, at least they have had some notice of the possibility that money may not be forthcoming the next round. But what is difficult to do without permanently damaging our ability to do business with universities, is to fail to support those for which we have made commitments. So if one makes some election as to where to take the saving, I suppose one would do his best to honor commitments and to make the cuts where they would do the least harm. This might not coincide with where the scientific priorities fall necessarily because you might be continuing some committed grants that were perhaps of a lower priority than the new ones that you were failing to start.

Mr. LAIRD. What I am concerned about is how such a reduction would be applied. Part of the present commitment to the international

banking community, which was concurred in not only by the President but by the Secretary of Treasury and the Chairman of the Federal Reserve Board, was an expenditure reduction of $8 billion plus a surtax of some 10 percent. This is all part of a package that there was an agreement on over the weekend. I am trying in my own mind to calculate where this $8 billion expenditure cut will lie. I can see how you can cut back perhaps $8 billion on obligational authority, but when you get into the expenditure area I think it is a more difficult problem.

I think that the committee will have to have a lot of good help from program directors to help at priorities. If we do not honor commitments, the programs might not be able to survive and it might take quite some time to get them geared up again.

Dr. SHANNON. Could I comment briefly on that, Mr. Laird?

If such a cut should come into being, it would be our responsibility to develop general guidelines within which the Institutes would carry on such reduction. Obviously this would be in association and consultation with them. We would have certain general intentions, the first of which would be to make the cuts in such a way as to minimize the impact on the integrity of the program. That would be the highest priority.

The second priority would be to minimize the impact on the stability of the institutions upon which these programs depend, both in their conduct of research and in those related activities that have to do with both the educational process and the delivery of services.

To achieve this it will be imperative to separate the things that have not been started from the things that are under way and consider whether—this might not always be the case—it would be wiser to defer new ventures and to maintain what one has.

I think one must look ruthlessly into this and determine what must have the higher priorities in regard to the integrity of the entire program, the integrity of the institutions and their relationship to other related functions.

We are talking here in terms of a 10-percent cut which would be $18.7 million for the Cancer Institute. This would be with relation to all aspects of the program and cuts of that order of magnitude would involve entire segments of the program. It cannot be done by paring a little here and a little there and attempt to keep all things going. The selection would have to be made in relation to programs that must go forward and those that can be held back. The priority or the guidelines that the Institute would be given would be somewhat along these lines.

Mr. LAIRD. Does the NIH have some instructions now to review these figures that you have presented in these very detailed justifications, which the committee has had before it now for several weeks?

Dr. SHANNON. No, sir; we have not had.

### DEPARTMENTAL REVIEW OF EXPENDITURE REDUCTION

Mr. LAIRD. Is the Department engaged in a review?

Mr. CARDWELL. The Acting Secretary has been advised of the President's interest in determining the effect of further cuts. He has asked him to provide him with some information which is now being developed. It is being developed at the Secretary's level.

Mr. LAIRD. Does this effort ever get down to the people at the operating level?

Mr. CARDWELL. Yes, it does.

Mr. LAIRD. Are these recommendations coming from the Secretary before there is any recommendation from the National Institutes of Health or from the operating bureaus?

Mr. CARDWELL. Thus far I do not think they have asked for these kinds of details.

Mr. FLOOD. Who are "they"?

Mr. CARDWELL. The President and his staff. In terms of overall impact on the department. In other words, a look at research as a whole, a look at the development of a support manpower and the support of institutions as a whole.

Mr. LAIRD. If you make recommendations as to research as a whole, does not the National Institutes of Health have any voice in that?

Mr. CARDWELL. I would think that they could and should. I think it depends on how it is done and just what the specific questions are. At this hour I am not familiar with all of the details and do not know exactly how it is going to be handled.

Mr. LAIRD. You think they will become involved with the new budget reappraisal?

Mr. CARDWELL. It all depends. For example, in the application of H.R. 888, which required a reduction of over $700 million in HEW, this was done without affecting the basic research programs of the National Institutes of Health. You used the figure of 10 percent. I doubt that we could take another 10 percent reduction against HEW as a department and not affect NIH.

Mr. LAIRD. I do not know how you could not affect NIH unless you cut back severely in the grants to the States in this budget.

These justifications have been very well worked out and, and I think it is fine for us to go ahead and have these hearings. But it would seem to me this committee should have the information currently being developed so we do not come out here with a bill that is based on justifications that are completely out of date.

I just learned of this review this morning.

Mr. CARDWELL. I am not privy to what is going on. I am not privy to the President's plan. It would be my guess, however, that if he has not already been in consultation with the chairman of the full committee he will be. I would be much surprised to find he has not. And I would think when they develop a plan it will be put before the committee and the individual members of the subcommittees.

Mr. LAIRD. I would like to have the information available as soon as possible so that in the course of these hearings we would be able to ask some questions about these new figures.

Mr. CARDWELL. It is possible they might propose a technique similar to the House Joint Resolution 888, which dealt with obligations and took into account congressional action it was applied on a postcongressional action basis. I do not know. That is one technique. It is my personal opinion if that one is going to control, his best control point in dealing with the Congress is obligations.

If your ultimate objective, as it certainly is, is to reduce expenditures, you must have control devices, and the control of obligational authority is a better device than a straight control on expenditures.

Mr. LAIRD. It is easier to control obligations but the President talks about expenditures.

Mr. CARDWELL. Any limitation on obligations is bound to produce an effect on expenditures. I do not know just what he had in mind. I am not that familiar with it.

RESEARCH IN SOLID TUMORS

Mr. LAIRD. Dr. Endicott, last year in our committee report we made reference to the work being done by the National Cancer Institute in the field of supporting research in solid tumors. Were you able to follow through on the recommendations of the committee report last year?

Dr. ENDICOTT. Yes, sir. I think that we are finally reaching a point scientifically where we have some handles for getting on with this problem. The evidence is accumulating very rapidly that the effectiveness of drugs in the treatment of the rapidly growing tumors like leukemia, which is not usually referred to as a solid tumor, is very dependent on getting the dosage of drugs carefully regulated to the cycle of cellular reproduction.

Mr. FLOOD. What is solid tumor?

Dr. ENDICOTT. That would be a tumor which produces a solid or semisolid single mass. Acute leukemia is characterized by a flooding of the whole bloodstream with the leukemic cells. So a breast tumor, for example, would be a solid tumor, local solid palpable mass. That is what they usually talk about when they talk about solid tumors. In fact, when you talk about solid tumors, you are talking about most other kinds of tumors except leukemia.

These tumors for the most part grow much more slowly and we have found it difficult to develop a laboratory model in which we can examine the cell cycle of the more slowly growing tumor.

Mr. FLOOD. Mr. Laird's original question referred to the report of last year and he asked you what you have done about that since then? Would you address yourself to that.

Dr. ENDICOTT. I am sorry if it was not responsive, sir. We have been working primarily in the laboratory to develop laboratory models in which we could examine the dependence on schedule of the dose in slowing growing tumors. At the same time, we have been trying to plan a series of studies in man in which this same phenomenon can be examined. If we have to do it in man without experience in a laboratory model, we will be going at it somewhat blindly and we feel we can make more rapid progress by concentrating on the laboratory studies which are relatively inexpensive before we launch a series of studies in man which are quite expensive and take a long time.

ATTITUDE OF PHYSICIANS TOWARD NIH RESEARCH

Mr. LAIRD. About 6 or 7 years ago I believe, this committee discussed the nonacceptance of some people in the medical profession of some of the work being done by the National Cancer Institutes and other Institutes of NIH.

I was present when a report was recently made by the House of Delegates of the AMA, in which the practicing physicians seemed to

take a different attitude. First, does that change of attitude carry over pretty well with the other health professions? And then I would like to ask Dr. Shannon to comment on this situation regarding the other institutes.

Dr. ENDICOTT. There is a very noticeable change in the attitudes of the physicians on medical school faculties toward clinical investigation in the cancer field and this I think is an outgrowth of the chemotherapy program. The treatment of advanced cancer is still experimental, but it is being carried out in many institutions across the country and it is getting out into the actual community. I mean this is research which is involving patients not just in the medical school, but patients all over the country who may go to the medical school to get started on the drug, but they come back and are taken care of at home by their own doctor. This kind of contact, I think, cannot help but change attitudes of the practicing physicians toward research programs because they can see concrete evidence in their own practice of benefit to their own patients. And I think this same attitude rubs off on the paramedical personnel, the nurses and other health personnel that work with the doctors.

I would say this: The climate is certainly warming up.

Mr. LAIRD. Do you want to comment, Dr. Shannon?

Dr. SHANNON. Yes.

I think it is a very perceptive comment, Mr. Laird. I think the experience of some of the other institutes is much along the lines Dr. Endicott indicated. During the past decade there has been a broad acceptance for a wide range of cardiovascular surgery. True, the surgeon has dealt with it, but the physician deals with a wide variety of cardiovascular defects. He has seen specific types cured by drugs. He has seen, in the past decade, a host of new viral vaccines which provide some immunity to common and important infections. He has acquired the ability to control hypertension in his own patient by new drugs. He has seen that it is possible to control arteriosclerosis, hardening of the arteries. He has seen the application of monitoring devices to patients with acute coronary disease through the widespread use of drugs and of coronary-care units, and how this can reduce mortality by as much as 50 percent.

He has been greatly aided by the automation of diagnostic procedures. Coronary units are now available in many hospitals across the country, not only the university hosiptal but the community hospital. So that he now has concrete evidence of the direct application to the patients of research which has improved diagnosis and treatment of disease.

I think it is because of the combination of these advances in many fields that he is, indeed, changing his attitude about the great importance and the very practical nature of biomedical research and investigation.

### PRESIDENT'S LUNG CANCER TASK FORCE

Mr. LAIRD. Dr. Endicott, you were appointed last year as Chairman of the President's Lung Cancer Task Force?

Dr. ENDICOTT. Yes.

Mr. LAIRD. I would like to know how this work is being funded?

Dr. ENDICOTT. The work at the present time is in the planning stages and being funded out of our normal funds for program direction.

Mr. LAIRD. Is this funded out of the funds of the National Cancer Institute?

Dr. ENDICOTT. Yes, sir.

Mr. LAIRD. Where did you get the money to finance this last year? I cannot find in last year's justifications anything that sets forth the funding of the Lung Cancer Task Force.

Dr. ENDICOTT. What this amounts to has been travel of consultants, sir; and this shows in the budget line item in the area of review and approval or in program direction. We have travel funds in connection with both.

Mr. LAIRD. Where is that in the justification?

Dr. ENDICOTT. There is a discussion of the Cancer Task Force on pages 44 and 45 of the justifications. As I say, this past year has been one of planning. We are proposing to begin operations next year and are requesting funds for personnel and for contracts. But this year we have been in the planning stage. That has just come out of our regular money.

Mr. LAIRD. This justification reads as though you are going to be in the planning stage for the next 12 months.

Dr. ENDICOTT. I will admit it is not a very large operation, but it is a beginning.

Mr. LAIRD. When I heard the announcement made on the Lung Cancer Task Force I thought it was a massive attack on cancer. I remember watching the announcement on television and also reading about it in the newspapers. I thought this was a massive program that was going to go forward promptly.

Dr. ENDICOTT. I must confess I entertained hopes that we would be able to move more rapidly than we will be able to.

Mr. LAIRD. It is a budgetary consideration then, it is not the fact you have not been able to do the planning?

Dr. ENDICOTT. It would have taken the better part of this year in planning anyway, but we could move more rapidly if we had funds next year, of course.

Mr. LAIRD. In 1969 what was the request of the Lung Cancer Task Force that was made to the Secretary?

Dr. ENDICOTT. The recommendation of the task force and of the National Advisory Cancer Council was that the budget for the first year of operation be $10 million. That would be in the 1969 budget. The task force began to operate in August and it was my feeling that it would have been unrealistic to have asked for a supplemental appropriation. We could not have gotten things started probably until the fourth quarter of fiscal 1968. So we did not request a supplemental, but we did make a recommendation, which went forward to the Surgeon General in November, of $10 million for inclusion in the 1969 budget.

Mr. LAIRD. Did that go forward to the Bureau of the Budget?

Dr. ENDICOTT. I do not think it did, sir. It arrived too late in the budget cycle. There were already guidelines and directives which made it infeasible, I think, to send it forward at that point.

EFFECT OF PROPOSED CUTBACKS ON DEPARTMENT'S BUDGET SUBMISSIONS

Mr. LAIRD. Mr. Chairman, as we go over these justifications, it seems to me that after this weekend they are a little out of date. I hope when the Department has finished its review we would be privy to such information that they have before we get into the mark-up of this bill.

Mr. FLOOD. Mr. Laird, I am not clear about what you mean by this weekend. I suspect you are talking about the new proposal for the gold market to be under a dual system, which is the only thing I think of, with one exception, that was dramatic on the weekend. But I cannot see where that would have much to do with these justifications.

Mr. LAIRD. I feel, if there is going to be reductions totaling some $8 billion in expenditures in the nondefense area, this committee should at least have an opportunity to look them over. I am not too satisfied that the priorities set by the Department might be the same priorities that this committee would want to set. I hope that when that information is available we will at least be able to look it over.

Mr. FLOOD. I do not think anybody would have any quarrel with that. I would include myself in that request.

Mr. CARDWELL. May I make a comment?

Mr. FLOOD. Yes.

Mr. CARDWELL. The question is the extent to which a specific plan is going to be developed and by whom. I want to make it clear the Department is not as of this hour developing a plan. It may have since I came up here this afternoon received orders to do so; I do not know.

Mr. FLOOD. I was referring specifically, and I think Mr. Laird was, to the duality of the operation of the gold system and the fiscal implications thereof.

Mr. LAIRD. I want you to know I was not referring, by the events of this weekend, to Senator Kennedy's announcement.

Mr. FLOOD. I said there were two dramatic things, but I took for granted the one you had in mind had reference more to gold. But I have difficulty in seeing where this proposed or suggested duality of the gold operation affects justifications.

Mr. CARDWELL. The point is that the President did refer to a program of reductions in domestic expenditures which would become a part of the package. That is the reference.

Mr. LAIRD. Along with a tax increase. And this was agreed upon by the various central banks that were represented. This is one of their requirements.

Mr. CARDWELL. That is what the papers said.

Mr. LAIRD. They agreed to this change in the rules regarding the role of gold with the understanding that the expenditure reduction would go through and a tax increase would be part of it. It was all part of the agreement they were able to work out.

Mr. CARDWELL. I think the point we would like to make is we do not want the President's announcement about further reductions in expenditures to shake the credibility of the budget we have sent up here. It does represent the priorities that were arrived at in concept between the agencies themselves, the Secretary's Office, the Bureau of the Budget, and the President, and I think it is too early to determine

and advise you as to what effect further reductions might have on HEW. I do not know.

But if it is decided they have an effect on HEW, I feel confident the President will tell this committee, and I would just like to reinforce that statement, that when it is determined and the extent to which it affects HEW, we will bring it to your attention promptly.

Mr. LAIRD. That is all I ask for.

Mr. FLOOD. I think you have a right to ask, and I join you.

Mr. CARDWELL. I do too, and I do not want to deny it.

## LUNG CANCER TASK FORCE

Mr. NATCHER. Dr. Endicott, when did you first set up a lung cancer task force?

Dr. ENDICOTT. I do not recall exactly but I think we had our first meeting last August.

Mr. NATCHER. I believe you stated to Mr. Laird that as far as the funding of this project is concerned it is only a small amount?

Dr. ENDICOTT. The only funding that has gone into it up to now has been two meetings of the task force and one meeting of the cigarette work group. The rest has all been staff work.

Mr. NATCHER. Dr. Endicott, was there a forerunner of the 10-member task force which you announced on August 17, 1967?

Dr. ENDICOTT. The only forerunner would have been a small group of men in my own office who were developing some tentative plans to present to the task force.

Mr. NATCHER. Do you mention anywhere in the justifications that previously a similar task force or a task force along this line had been in operation or had been set up?

Dr. ENDICOTT. Well, sir, there had not been one. I didn't mention it in the justifications; no, sir. The chronology, if I may, was as follows: At a regular meeting of the Advisory Cancer Council in November 1966 the Council recommended to me that I establish three task forces, one for cancer of the colon and rectum; one for cancer of the prostate and bladder; and one for cancer of the lung; and recommended that we accept the responsibility for management of the lung cancer task force, a direct operation, and that we request a university to undertake the management of the other two.

I was in the process of carrying out this recommendation of the Council when, in his health message, the President directed the Secretary of Health, Education, and Welfare, to set up a task force.

Of course with this directive I stopped any further action until I found out how this was going to be handled. I felt it would be inappropriate to have two task forces, one created by the Secretary and one by me. So although I had already gotten the consent of Dr. Kotin, who headed the Division of Environmental Health Sciences, to chair the task force, several things happened. He moved away, the thing happened in the health message, and by the time we got it all sorted out and a task force named it was August.

Mr. NATCHER. In making a report to the President last July did you show that $1.5 million was allocated in fiscal year 1967 from the National Cancer Institute to a lung cancer task force? Did you show that figure of $1.5 million?

Dr. ENDICOTT. I believe, yes, sir. As I recall it, there was a pie chart which indicated that. This represented the best estimate I could make at that time of the amount of money that we were spending in grants for lung cancer—related scientifically to the kinds of activities that the task force would concern itself with, but not controlled in any way by the task force. Some of these may become a part of the operating package of the task force when it becomes operational.

Mr. NATCHER. Was this $1.5 million actually allocated in 1967 and used for this purpose?

Dr. ENDICOTT. Yes, sir. And it included experimental therapy in the treatment of lung cancer, a study of steroids and drugs together with surgery used in the treatment of cancer.

Mr. NATCHER. What was the task force you announced in August supposed to do?

Dr. ENDICOTT. It is primarily a planning and coordinating group of experts. I think when we get through the planning stage we probably will change the makeup of the task force because in our experience the really effective task force is made up not of advisers but of people who are actually doing the work. So as we move out of the planning stage and into the operational stage I would expect there will be a substantial change in the composition of the task force.

MEMBERSHIP OF THE TASK FORCE

Mr. NATCHER. Can you tell me the names of the members of the task force? I believe there were 10?

Dr. ENDICOTT. Yes, sir.

Mr. NATCHER. If you do not have that you may supply it for the record at this point.

Dr. ENDICOTT. Yes, sir.

(The information follows:)

MEMBERS OF THE LUNG CANCER TASK FORCE

Dr. Kenneth M. Endicott, *Chairman*

Dr. Paul Talalay, professor, Department of Pharmacology, Johns Hopkins Hospital, Baltimore, Md.
Dr. Emmanuel Farber, professor and chairman, Department of Pathology, University of Pittsburgh, Pittsburgh, Pa.
Dr. Juan del Regato, director, the Penrose Cancer Hospital, Colorado Springs, Colo.
Dr. George B. Hutchison, Department of Radiation Therapy, Michael Reese Hospital and Medical Center, Chicago, Ill.
Dr. Bayard H. Morrison III, assistant director, National Cancer Institute.
Dr. Julius Wolf, chief, Medical Services and associate chief of staff, Bronx Veterans' Administration Hospital, Bronx, N.Y.
Dr. Paul Kotin, director, Division of Environmental Health Sciences, NEHSC, Research Triangle Park, N.C.
Dr. Carl Baker, scientific director for etiology, National Cancer Institute.
Dr. Hans Falk, associate scientific director for carcinogenesis, NCI.

LIAISON MEMBERS

Mr. Walter James, vice president for Public Education, American Cancer Society, Inc., 219 East 42d Street, New York, N.Y.
Dr. Ashbel C. Williams, American Cancer Society, Inc., 219 East 42nd Street, New York, N.Y.
Dr. Roy Lester, American Medical Association, One Farragut Square South, Washington, D.C.

Dr. Frederick W. Irish, chief, Division of Scientific Opinions, Bureau of Deceptive Practices, Federal Trade Commission, Washington, D.C.
Dr. H. D. Bruner, Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, D.C.
Dr. Sam R. Hoover, Assistant Deputy Administrator, Nutrition, Consumer and Industrial Use Research, Agricultural Research Service, Department of Agriculture, Washington, D.C.
Dr. Clarence Cook Little, scientific director of the Council for Tobacco Research, 633 Third Avenue, New York, N.Y.

Mr. NATCHER. Dr. Endicott, are any of these gentlemen members of the former task force or the task force that was designated ahead of the one you announced in August?

Dr. ENDICOTT. Are you perhaps, Mr. Natcher, referring to the committee that drew up the Surgeon General's report?

Mr. NATCHER. Did you announce that as a task force?

Dr. SHANNON. I would like to clarify something here. To my knowledge, first may I say the Cancer Institute has been interested in lung cancer for many years and has supported research in this field for many years. I think too much may be taken as being analogous between supporting research on lung cancer and creating a task force. A task force is an administrative device to bring together the many skills necessary to develop an orderly plan for the examination of a problem, for the central planning of the future course of studies and for future funding. In addition, it can provide the necessary program analysis and surveillance of development.

Mr. NATCHER. Did you have a task force ahead of this one, Dr. Shannon?

Dr. SHANNON. No.

Mr. NATCHER. Is it not true that you had one ahead of this one?

Dr. SHANNON. To my knowledge, no, sir. There was an activity but it was not designated as a task force.

Mr. NATCHER. You did not have it designated as a task force?

Dr. SHANNON. Not to my knowledge. Dr. Endicott can perhaps answer that.

Dr. ENDICOTT. That is why I asked if you were referring to the committee that drew up the Surgeon General's report, because this task force announced in August is the only one I am aware of.

Mr. NATCHER. No task force prior to that time.

Dr. ENDICOTT. Not that I am aware of.

Dr. SHANNON. There was work in lung cancer going on and any expenditure prior to that time would have direct relevance to cancer of the lungs.

PROGRESS OF LUNG CANCER RESEARCH

Mr. NATCHER. You recall our committee last year indicated in its report that it was interested in hearing what progress any lung cancer task force that might be appointed was making with respect to the causes of lung cancer. That is contained in our report beginning on page 21 and continuing over to page 22, and a statement concerning the importance of this matter. Can you give us any report other than the statement you have given the committee that not much has been done?

Dr. ENDICOTT. Well, sir, there has been relatively little research work but a lot of work has been done in planning what we should do when we do start, and this has been very time consuming and we are not anywhere near the end of this stage. We are giving first attention to the cigarette problem and to examining the possibilities of producing a less hazardous cigarette. A work group is actively discussing this. They will be meeting fairly frequently in the coming months.

One of the problems is deciding on what kind of criteria you will use to determine whether you are making progress or not in modifying the filter, the tobacco, or whatever it is you are attempting to do to make the cigarette less hazardous.

MISSION OF LUNG CANCER TASK FORCE

Mr. NATCHER. Dr. Endicott, let me ask you, is the lung cancer task force which was named on August 17, 1967, directed to pursue research into the causes of lung cancer, or was it primarily set up to prevent cigarette smoking and to look into a less hazardous cigarette? Which would be the road you intend to travel?

Dr. ENDICOTT. Well, the task which I have assigned to the task force is to examine the whole problem of lung cancer and to recommend to me what avenues of research they think would be the most productive in bringing lung cancer under control. Part of the efforts is certainly going to be directed toward some improved method for early detection. Efforts must be made to improve the effectiveness of treatment. A 5-percent cure rate is simply frightful. So a substantial part of the efforts will have to go into the question of the clinical management of the disease when it occurs. The rest is aimed at trying to prevent the disease. We have already identified some areas where we feel real progress can be made from a research standpoint. I will try to enumerate them.

First, of course, is the cigarette.

Second is a series of exposures which occur which we have already identified in industry. There are probably others we do not know about but we have identified certain types of exposure in industry which are clearly associated with an increase in lung cancer. The problem of the role of atmospheric pollution has to be examined intensively. There is really no doubt in my mind that this is making some contribution to the problem.

Another possibility which cannot be excluded is that viruses may play a role and may set the stage, so to speak, and that these other things—industrial exposure, atmospheric pollution—may trigger the reaction from the stage being set by viruses, but this must be actively explored.

Then, finally, of the workers in the factories exposed to the dust and fumes only a relatively few of them get cancer of the lung, just as relatively few cigarette smokers get cancer of the lung, and there is obviously something here which determines whether you do or you don't. If we could really find what this is we might be able to attack the problem at that point by doing something to modify individual susceptibility.

So my charge to the task force was to look at the whole problem, tell me what are the possibilities, what they regard as the most likely to be

productive, and which they feel are the most feasible. That is the charge to the task force.

SELECTION OF MEMBERS OF LUNG CANCER TASK FORCE

Mr. NATCHER. Did you place on the task force any of the doctors or scientists who disagree with any opinion or theory which you have as to the cause of lung cancer so far as cigarette smoking is concerned? Do you have anyone on the task force who would come in that category?

Dr. ENDICOTT. It certainly was not one of the criteria that I used in attempting to select the group. I selected men whom I regarded as being outstanding in their particular field of research.

Mr. NATCHER. Did you select Dr. Moore? Is he a member of the task force?

Dr. ENDICOTT. Dr. Moore? No.

Mr. NATCHER. You know the Dr. Moore that I refer to.

Dr. ENDICOTT. I assume you mean the one from Roswell Park. No; he is not a member.

Mr. NATCHER. Did you select anybody from the tobacco industry for the task force?

Dr. ENDICOTT. I invited liaison representatives from the tobacco industry's research committee, and the man who has come has been C. C. Little.

Mr. NATCHER. And the former president of the University of Michigan?

Dr. ENDICOTT. Yes, and of Maine, too.

Mr. NATCHER. A right unusual gentleman.

Dr. ENDICOTT. Dr. Hockett has also been designated, but as I recall it, he was unable to attend.

Mr. NATCHER. What part would they play as far as the task force is concerned? You did not name them as members?

Dr. ENDICOTT. I invited liaison representation from the tobacco industry's research committee, from the American Medical Association, and from several other Federal agencies including Agriculture and the Federal Trade Commission, primarily as a communications device so that they could keep their people who have an interest in this problem informed as to what we were doing. In terms of industry participation, the real work in the tobacco area, the really detailed planning, will be carried out by a work group on a less hazardous cigarette, and I have invited several members from the tobacco industry to be members of that work group. In the end, there probably will be three or four men from industry.

RESEARCH FOR A SAFER CIGARETTE

Mr. NATCHER. Last year, if you will recall, you stated you were not in a position at that time to recommend a specific way to make safer cigarettes. Are you in a position at this time to make any recommendations along that line, Dr. Endicott?

Dr. ENDICOTT. No, sir, I am certainly not. I would say this, though, that I think it is technically feasible to do so.

Mr. NATCHER. Dr. Endicott, since research has apparently pro-

duced little information that bears on what a filter should do, how would you evaluate any new development in cigarette filtration?

Dr. ENDICOTT. This is at the heart of the problem I have put to the group on which the representatives from industry, I hope, will work, and that is, what set of criteria, biological measurements, can we accept as indicating the degree of hazard. That is, if you are going to change filters, or if you are going to add a filter to a cigarette in the first place, if you are going to be able to determine that this has improved something, first you have to have some criteria as to what constitutes improvement. There is quite a variety of biological tests that can be made and there is at this point in time far from a consensus as to what they mean and which ones we should do and which ones we should rely on and what weight we should give them. A whole long string of tests could be done and the problem they are wrestling with is which ones should be used and what weight or value should be assigned to the results.

Mr. NATCHER. Just assuming for the purpose of argument that the task force decides it has found a filter which would make cigarettes safer, what would you do about it? Would the Government seek legislation to make such a filter mandatory? Would the Government manufacture the filter? What would you recommend assuming the task force would come up with a conclusion such as I have just indicated?

Dr. ENDICOTT. If the task force came to me tomorrow and said, "We have concluded you should put such-and-such a filter on cigarettes," I would send them home because I would know that as of now they have not arrived at any criteria with which they could convince me. So the question is an iffy one but if I understand the intent of your question, my feeling is that the proper role in this effort, the proper role for the lung cancer task force and the National Cancer Institute, is primarily a role of biological evaluation, and that if anything is to be accomplished it will probably have to be accomplished by working with individual companies who themselves are attempting to modify their own products, and our role will principally be one, as best we can, of providing the biological tests against which they can measure the effectiveness of their manipulations of the product.

I had not thought it likely that the lung cancer task force would itself become involved in the manufacture of filters or of cigarettes or the modification of tobaccos, tobacco culture and curing. That is not our area of competence or our cup of tea. We thought the contribution we could make was a biological yardstick.

Mr. NATCHER. Dr. Endicott, if you are sure that cigarette smoking causes lung cancer, can you tell the committee just how or by what mechanism cigarette smoking causes this disease?

Dr. ENDICOTT. No, sir, I cannot.

### OCCUPATIONAL HAZARDS AND LUNG CANCER

Mr. NATCHER. Now, Dr. Endicott, you refer in the justifications to identification and modification of industrial-atmospheric-occupational hazards. Have they been identified?

Dr. ENDICOTT. We have identified some of them. One is asbestos. Another is beryllium. These are both dusts. Another are the oxides of chromium. Another are certain nickel dusts. Another are fumes

given off in the coking process. Workers in coking plants—top workers they call them who have something to do up near the top of these big coke ovens—have an alarmingly high incidence of lung cancer, presumably due to the fumes and poor ventilation of the buildings. We have identified those. There are others we have not identified but we know there is pay dirt there.

Mr. NATCHER. Let me read a portion of a letter written last year by Dr. W. C. Hueper, former Chief of the Environmental Cancer Section of the Department of Health, Education, and Welfare:

> Lung cancer accounted for several decades since 1870 for approximately 70 percent of the deaths among the radioactive ore miners in Schneeberg, Germany. When this warning concerning similar occupational cancer hazards for the American pitchblende miners was sounded in 1948, both governmental agencies (PHS and AEC) chose to ridicule its scientific soundness and accused the environmental cancer expert of the National Cancer Institute of using "bad judgment." They blocked forcefully the conveyance of the information available on this cancer hazard for over 60 years, to members of the medical profession of the State of Colorado.
>
> When now after 20 years of procrastination the embarrassing evidence cannot be suppressed any longer, some pliable members of the Public Health Service try to obscure and confuse this alarming issue by propagating the scientifically unsound claim that the lung cancers among the American uranium miners are not caused by the inhalation of radioactive gases and dusts but by excessive cigarette smoking. This allegation is advanced despite contradictory epidemiologic evidence provided from American and Canadian sources and despite the fact that about 200 German radioactive ore miners succumbed to lung cancer between 1870 and 1910 when cigarette smoking was either nonexisting or relatively rarely indulged in and when lung cancer among the general population was rather rare.
>
> The persistent and wanton disregard of the various well-established and internationally recognized occupational and industry related respiratory carcinogens as causes of significant lung cancer hazards by the Public Health Service has resulted not only in a regrettable neglect in achieving a practically feasible controll of such hazards but also in depriving widows and orphans of occupational lung cancer victims of workmen's compensation to which they are entitled by law. Experiences of many years as a medicolegal expert of occupational cancer hazards in litigations of this type have provided many illustrations of the pernicious effects of the noted misguided public health policies.

What was Dr. Hueper's position when he was with the Public Health Service?

Dr. ENDICOTT. He was head of a section on occupational or enviromental cancer.

Mr. NATCHER. What do you have to say about these charges he levels in his letter? Are you acquainted with the letter?

Dr. ENDICOTT. No, sir; I am not acquainted with the letter. But it is like a hundred others he has written in all sorts of fields. I am very familiar with Dr. Hueper's letters, but not that particular one.

Mr. NATCHER. How long was he in the Department of Health, Education, and Welfare? Can any of you tell me?

Dr. ENDICOTT. It was quite a long time. I would have to look it up in the record, but I should think it was at least 20 years.

Mr. NATCHER. Who occupies the position that he held, who is in that position now?

Dr. ENDICOTT. We are so completely reorganized by now that the position he held no longer exists.

Mr. NATCHER. Who occupies a position similar in authority and assignment?

Dr. SHANNON. Dr. Kotin, who is now Director of the Division of

Environmental Health Sciences took over this function when he came to NCI. Dr. Baker has succeeded Dr. Kotin who is now in North Carolina.

Mr. NATCHER. The committee will adjourn until 10 o'clock in the morning.

TUESDAY, MARCH 19, 1968.

Mr. FLOOD. Mr. Natcher?

CANCER TASK FORCE

Mr. NATCHER. Dr. Endicott, yesterday, as you will recall, we discussed somewhat in detail the task force that was set up in August of last year. In order there may be no misunderstanding about the purpose of the task force and how it was set up and just what the functions are to be, I am wondering if at this point you will explain to the committee just what brought this on, what was the background for it, and what do you have in mind from the standpoint of this task force. This was under consideration long before any announcement was made downtown about a task force. Is that correct, Dr. Endicott?

Dr. ENDICOTT. Yes, sir; that is correct.

Mr. NATCHER. I wonder if you would explain to us just exactly what transpired. To save time, Mr. Chairman, suppose, Dr. Endicott, if you would at this point in the record place a short statement on the background, what you had in mind, where you propose to travel insofar as the task force is concerned.

Dr. ENDICOTT. Yes, sir.

(The information follows:)

STATEMENT CONCERNING THE LUNG CANCER TASK FORCE

During the past decade NCI has developed and used a variety of management and planning techniques as a means of focusing on specific cancer problems. Among them is the task force, which serves to bring together for discussion and planning, scientist and physician experts in various aspects of a particular disease problem. A task force may or may not have funds earmarked in support of its activity. In either case task forces are dependent for effective action on established programs of the Institute which relate to the area of task force interest but are not controlled by the task force, that is, research grants, the chemotherapy program, and so forth.

The acute leukemia task force, established in 1962, was the first of the NCI task forces. The members drawn from Government and nongovernment institutions by identifying important problems and possible solutions have greatly facilitated NCI's increasingly successful research attack on acute leukemia, particularly the acute leukemia of childhood. Since 1962, a considerable number of other task forces have been established for diseases such as the lymphomas, chronic leukemias and breast cancer. Task forces are generally constituted only when it is felt that enough basic scientific information is available to permit formulation of a cohesive research program directed at solution of key problems relating to the disease.

The NCI's concern about the increasing number of lung cancer deaths was sharpened by the 1964 report on smoking and health by the Surgeon General's Advisory Committee. Although a variety of research activities relating to the etiology, diagnosis, and treatment of lung cancer has been supported by NCI (at a level of about $1.5 million in fiscal year 1967), the National Advisory Cancer Council in November 1966, feeling that a concerted research attack on lung cancer could be made, recommended that the NCI establish a lung cancer task force. At the same meeting the Council recommended that two study groups be established, one for prostate and bladder cancer and the other for colon-rectum cancer.

In February 1967, shortly after some preliminary planning had been initiated, the President in his health message directed the Secretary, HEW, to establish a lung cancer task force to plan and implement a research program through which lung cancer could be prevented or controlled. Accordingly, as staff planning continued, a 10 member task force was constituted under the aegis of the NCI and with Dr. Kenneth M. Endicott, Director, NCI as Chairman, held the first meeting August 16, 1967. With the assistance of completed staff work, the group considered in broad terms the dimensions of the problem and a variety of research approaches that could be followed. The second meeting of October 8, 1967, was devoted to more detailed examination of specific research options and a preliminary consideration of budget. The second meeting was also attended by the invited liaison representatives of a number of concerned organizations, including American Cancer Society, American Medical Association, Federal Trade Commission, Tobacco Research Council, Atomic Energy Commission, and Department of Agriculture.

At the second meeting the task force agreed that primary effort should be given to the development of a less hazardous cigarette and that a work group should be selected to consider the appropriate research approaches that should be made to accomplish this. A work group, which includes scientists from the tobacco industry as well as the academic community and the Government, has been selected; their first efforts will be addressed to determining the makeup of biologic and chemical assay systems which will permit the meaningful comparison, in respect to aspects of potential hazard, of cigarettes which incorporate various tobaccos, filters, and other devices.

The task force also agreed that of the other aspects of the lung cancer problem, occupational-industrial-atmospheric hazards and improved diagnosis and detection should be the subjects of major research investigations.

A first year budget of $8.5 million to permit personnel recruitment and implementation of key projects in each of the main research areas was recommended. At the October 1967 meeting the National Advisory Cancer Council approved the recommendations of the lung cancer task force, and further recommended that the Institute collaborate with the National Clearinghouse on Smoking and Health in an educational program designed to provide, to the public, information concerning lung cancer.

Thus far the lung cancer task force has been engaged entirely in planning activities and only a small amount for travel has been required. No funds were appropriated for program activities in fiscal year 1968. For fiscal year 1969, $1.4 million has been requested as a line item.

It is anticipated that appropriation of this amount will permit initiation of the program by making possible recruitment of staff and startup of high priority projects, particularly those relating to development of a less hazardous cigarette.

DEVELOPMENT OF SAFE CIGARETTE

Mr. NATCHER. Now, Mr. Endicott, you mentioned in the justifications the development of an assay system which will form the basis for the eventual development of a less hazardous cigarette. What do you have in mind?

Dr. ENDICOTT. We have in mind a set of tests, some of them chemical and some of them biological, to measure from a biological standpoint the biological effects of cigarette smoke, and in this way sort of assay the biological effects in changing the cigarette, the filter for the tobacco, whatever, and then testing the smoke from the product in question to see whether the biological effects have been diminished or increased by that particular modification.

Mr. NATCHER. Would there be any conflict as far as this particular program is concerned( Dr. Endicott, in the program that Dr. Kotin intends to have under way at the Environmental Center and, as far as the task force generally is concerned; would there be a conflict?

Dr. ENDICOTT. No, sir; as a matter of fact, we are seriously considering locating that part of the task force program at the Research

Triangle and asking Dr. Kotin to accept the responsibility for managing it. In other words, it would be jointly financed but managed by the one division.

Mr. NATCHER. Dr. Endicott, why would you need additional money as far as the task force or any work along this line is concerned rather than to have additional funds for the environmental health sciences?

Dr. ENDICOTT. It could be handled in either way, sir.

Mr. NATCHER. Which would be the better way, Dr. Endicott?

Dr. ENDICOTT. Well, sir; I do not think it would make any difference really.

Mr. NATCHER. How much money do you have programed or do you plan to spend over the next 5 years through the lung cancer task force on smoking? Can you give us some idea about it?

Dr. ENDICOTT. We have prepared a 5-year forecast which I would be happy to supply for the record.

Mr. NATCHER. And with that forecast, let us have some idea as to the amount of money involved, please.

Dr. ENDICOTT. Yes, sir.

(The information follows:)

FIVE-YEAR FORECAST FOR THE LUNG CANCER TASK FORCE

A 5-year funding estimate for the lung cancer task force has been developed. A total of $31,898,000 and 55 positions are estimated for in-house and contract operations.

| | 1969 | 1970 | 1971 | 1972 | 1973 |
|---|---|---|---|---|---|
| Amount (thousands) | $1,400 | $3,823 | $7,002 | $9,239 | $10,434 |
| Positions | 22 | 32 | 42 | 50 | 55 |

On the basis of lung cancer task force and National Advisory Cancer Council action, several distinct research efforts are envisioned: (1) Development of a less-hazardous cigarette; (2) identification and modification of other environmental hazards; (3) host modification; (4) detection and diagnosis; (5) treatment. A program of public information in collaboration with the National Clearinghouse for Smoking and Health is also planned.

Initial emphasis will be given to development of a less-hazardous cigarette. Instrumental to this effort will be selection and establishment of biologic and chemical assay systems for comparing the hazardous potential of cigarettes embodying various tobaccos, filters, and other devices. Further development of this effort will require increase or creation of competence in biometry, pharmacology, pathology, data retrieval, and other areas.

At this stage of planning, no precise cost figures for any single phase of a lung cancer research program have been developed. Of the above 5-year estimate, it is reasonable to expect that at least 50 percent would be expended on the development of a less-hazardous cigarette.

Since the smoking and health problem logically extends beyond lung cancer to heart disease and chronic lung disease, it is anticipated that research into these areas will be conducted by other units of NIH if funds permit. It is possible that the entire research effort will be conducted and supported jointly by the National Cancer Institute, National Heart Institute, and Division of Environmental Health Sciences. The above estimates, however, pertain to a comprehensive program in lung cancer, and do not relate to the total smoking and health problem.

Mr. NATCHER. Last year this subcommittee was furnished considerable material relating to a safer cigarette. This was inserted in the record at the committee's request and I believe Dr. Kotin told us of plans for a research program which included formulation of a safer

cigarette. He referred to animal experiments involving cigarette smoking. He testified that his program would be directed at techniques for altering the condensate. He told us he planned to spend about $480,000 during this fiscal year in the area of tobacco and health.

He also told us, Dr. Endicott, that there were several other areas of interest, including air pollution, and he further testified he would not be proceeding from predetermined conclusions in any particular area such as smoking.

Now the question I have in mind pertains to Dr. Kotin's programs and the task force generally. What conclusions would be reached or what would be your line of work as far as how you intend to proceed and how Dr. Kotin intends to proceed along this particular line?

Dr. ENDICOTT. Sir, Dr. Kotin is a member of the lung cancer task force. We have agreed from the very beginning, before he accepted the post in North Carolina, there was a large area of research which would be of great interest and concern to both organizations, and that we must always plan together and work together very closely.

In the lung cancer field, with Dr. Kotin and Dr. Falk, who will be leaving my staff in June to join Dr. Kotin, are two of the very best men in this area of research in the world. And it is my feeling that because of their own personal qualifications, the work on the cigarette should be their responsibility.

It is obviously a major cancer problem and quite appropriate for the funding, part of the funding at least, to be in the Cancer Institute, but the actual program management I think should be placed where the best management is available.

Mr. NATCHER. Dr. Endicott, I assume that the National Cancer Institute continues to fund activities, directly, on smoking and lung cancer; is that correct?

Dr. ENDICOTT. Yes, sir.

Mr. NATCHER. With your permission, Mr. Chairman, I would like to ask Dr. Endicott two questions Mr. Smith left with me yesterday, and then I am through.

Mr. FLOOD. Yes.

### RESEARCH BY DR. OTTO WARBURG

Mr. NATCHER. Dr. Endicott, have we financially supported the work of the one-time Nobel Prize winner, Dr. Otto Warburg? Or maybe somebody else could handle the question.

Dr. ENDICOTT. It was before my time, but Dr. Warburg actually worked at the NIH for a time. And one of my scientists, Dr. Dean Burk, has almost, every year, gone to Germany during the summer to work with Dr. Warburg, but I do not believe that we have been providing financial support to Dr. Warburg since he returned to Germany. I think his support there is quite adequate from the German Government.

Mr. NATCHER. Is Dr. Burk attempting to substantiate or analyze Dr. Warburg's work?

Dr. ENDICOTT. Yes, sir; that has been his principal area of interest for most of his career.

Mr. NATCHER. Dr. Endicott, what progress has Dr. Burk made

and what is the significance of this particular work? Can you give us some idea as to what progress has been made?

Dr. ENDICOTT. Dr. Burk has done a great deal of very splendid research which confirms, in a number of different kinds of cancer, the original observation made by Warburg in one kind of cancer—that is that the metabolism, the chemical processes by which foodstuffs are oxidized or burnt, are different in cancer cells than in normal cells. This is not universally true. Dr. Warburg's theory has not been accepted as an essential feature of cancer. That is what the argument has been about—are all cancers this way or only some of them? And the main body of scientific opinion is that only some of them are, but there is no question that some are.

Mr. NATCHER. Thank you, Dr. Endicott.

Mr. FLOOD. Mr. Michel?

CANCER DEATH RATE

Mr. MICHEL. How many years back do we have accurate figures for the death rate attributed to cancer or various forms of cancer?

Dr. ENDICOTT. They go back a long way, but the accuracy is the problem. Not infrequently cancer is not diagnosed until an autopsy, and only a relatively small portion of the population actually is subject to autopsy.

Mr. MICHEL. You say in your testimony:

"We have reduced death from uterine cancer 40 percent in the last 25 years."

Dr. ENDICOTT. Oh, yes. I was thinking in much longer terms.

Mr. MICHEL. Let's talk about the last 25 years.

Dr. ENDICOTT. Right.

Mr. MICHEL. You say that despite steady improvement in the cure rate, the cancer death rate continues to creep higher year by year?

Dr. ENDICOTT. Yes.

Mr. MICHEL. How would these curves or lines or graphs be projected? The population is increasing; is the rate of death per thousand increasing or decreasing? In other words, what can we use as a benchmark, 5 years ago, 10 years ago? Are we really making significant progress, or is it just creeping along?

Dr. ENDICOTT. It is slow, but it is certainly progress. If you go back say 30 years, the crude death rate (that is just the number of deaths by diagnosis, not corrected for age or anything) for cancer as a whole was 124 per 100,000. It is now 152 per 100,000. When the statisticians begin to manipulate these numbers, they try to correct them for age and they correct them for a variety of other things, age distribution, sex, and so on, because part of this is related to the average age of the population. Risk of cancer is much greater in someone past 60 than it is in someone 10 years younger.

Mr. MICHEL. So the increasing life expectancy of all of us contributes then in part to that increase?

Dr. ENDICOTT. Yes. The rising number of cancer deaths in the country is partly due to an increasing population; partly due to an increasing number of people who are in the older age groups, because people are living longer. It is partly due—but I do not think this is

very important in the last 25 years—to improvements in diagnosis. We are diagnosing more of them.

Mr. MICHEL. In other words, in years past people who had cancer would not be diagnosed, and therefore they never fell within the statistical category as being a death attributed to cancer.

Dr. ENDICOTT. Right. But the experts, after correcting for all of these factors as best they can, maintain that there is still a very substantial residual increase in cancer which cannot be explained on any of those bases.

Mr. MICHEL. You predict this year that there will be 28,000 deaths as a result of breast cancer in women. How would that figure of 28,000 compare with the figure in the same category for 5 years ago? We have accurate figures as recently as 5 years ago, don't we?

Dr. ENDICOTT. Yes. I would have to check that. We could go back very accurately for about 30 years. And these figures are based on a sample population which we follow all the time and which permits us to extrapolate or interpolate between regular benchmarks, like the census, and the death statistics.

(Information follows:)

NUMBER OF BREAST CANCER DEATHS 5 YEARS AGO

Number of breast cancer deaths in 1963 was 25,000 as compared to 28,000 for 1968. For both periods, this amounted to 24 deaths per 100,000 population. Considering population growth, this represented a constant rate of breast cancer deaths during the past 5-year period.

Mr. MICHEL. How does our cancer death rate compare with countries that are as reasonably advanced as we are in the field of medicine? Is there any wide disparity?

Dr. ENDICOTT. There is a disparity; it is not what I would regard as a wide disparity. In all of the advanced nations, for example, cancer death rate is in the same place in the rank order list of causes of death. It is second to cardiovascular in all of the advanced countries.

Mr. MICHEL. Would there be any place on the globe or any country or area where there would be a marked difference of death rate; much less, for example, than ours? Could this be attributed to environment or something?

Dr. ENDICOTT. Oh, yes. The backward countries where there is a high death rate and the average lifespan, let's say is age 30—although their health statistics are miserable because of lack of doctors and what not—clearly cancer is not an important cause of death at all.

In places like Central Africa, it occurs, but as a cause of death it is simply not in the running with starvation, malnutrition of some sort, and a whole host of infectious and parasitic diseases we do not even have in this country.

RESEARCH FUNDS

Mr. MICHEL. Of this $187 million you are requesting, what portion would be for any kind of research? In other words, of the total of $187 million, how much are we talking about in total in the research field of one kind or another, basic applied grants and so forth?

Dr. ENDICOTT. It is all in research except for $11.6 million, and $4.4 million for training and fellowships respectively. The rest of this I would regard completely as research funds.

Mr. MICHEL. How much of this research then is contracted for?

Dr. ENDICOTT. The contract budget is roughly a third, $52 million.

Mr. MICHEL. $52 million would be contracted for?

Dr. ENDICOTT. Yes.

Mr. MICHEL. And this would be made up principally of what kind of contracts?

Dr. ENDICOTT. There would be contracts in four major areas. One, and probably the largest, certainly the oldest, is the drug development program, which is called chemotherapy.

Mr. MICHEL. And contracts entered into in that area would be with firms or individuals or both, or institutions principally?

Dr. ENDICOTT. There are drug development contracts in industry, there are a number of them in what you would call professional research institutions like Arthur D. Little or Southern Research Institute or Stanford Research Institute that have been set up to do contractual research.

Mr. MICHEL. Some of these would go back how many years?

Dr. ENDICOTT. Probably the oldest one would go back to 1956.

Mr. MICHEL. Is there a constant review of these to make sure we are getting our money's worth, or is this getting to be kind of automatic, since company A got a contract 2 years ago, they get to kind of leaning on it as a crutch and know they are going to keep getting it?

Dr. ENDICOTT. We caught a couple of them doing that and we pulled the crutch out. We have canceled many contracts over the years. They are reviewed every year. We have found some of the companies are consistent first-rate performers, others have not worked out at all well. There is a long string of contracts that we have canceled.

Mr. MICHEL. What are the other areas?

Dr. ENDICOTT. Another one is in the field of viruses of cancer and these contracts, although some of them are with industries that work in the vaccine production field, most of them are contracts with universities.

A third area is chemical carcinogenesis. This is the kind of research we have been talking about with Mr. Natcher in which you are testing chemicals for their effect in causing cancers. This is a mixture of university and industry and commercial laboratory contractors.

Then the fourth area is in the general field of statistics, biometry, and epidemiology and here the contracts are likely to be with Government agencies since they are the agencies which collect and maintain much of the statistical information. Some are agencies of the U.S. Government, some of State governments, and some of foreign governments. So the contractors in that area are mostly governmental.

Mr. MICHEL. Would you put in the record a list of the 10 largest research contracts for industry, for universities, and for individuals, the amount and what the project is?

Dr. ENDICOTT. Yes, sir; I would be glad to.

(The information follows:)

10 LARGEST RESEARCH CONTRACTS, SUPPORTED BY NCI, FOR INDUSTRY, UNIVERSITIES, AND FOR INDIVIDUALS

INDUSTRY

| Contractor | Contract number | Amount | Purpose |
|---|---|---|---|
| 1. Charles Pfizer & Co., Inc., Maywood, N.J. | 66-98 | $1,880,315 | Development of virus-cancer test systems, virus production, production of human virus-cancer cell lines; immunology. |
| 2. Bionetics Research Laboratories, Falls Church, Va. | 67-661 | 1,719,811 | Viral carcinogenesis and cocarcinogenesis in primates. evaluation of fluorescent antibody tests. |
| 3. Charles Pfizer & Co., Inc. | 64-50 | 1,416,710 | Drug development and evaluation. |
| 4. A. D. Little, Inc., Cambridge, Mass. | 65-61 | 1,356,190 | Drug development and evaluation, screening, experimental therapeutics, pharmacology. |
| 5. Southern Research Institute, Birmingham, Ala. | 65-594 | 1,332,790 | Primary and secondary screening and methodology. |
| 6. Microbiological Associates, Inc., Bethesda, Md. | 64-911 | 1,176,000 | Chemotherapy investigations; experimental therapeutics, antiviral, pharmacology, biochemical, immunology. |
| 7. Dow Chemical Co., Midland, Mich. | 65-1045 | 842,034 | Research and development of biohazards containment facilities. |
| 8. Bristol Laboratories, Syracuse, N.Y. | 64-1159 | 699,463 | Development of antibiotics; screening and methodology. |
| 9. Stanford Research Institute, Menlo Park, Calif. | 64-500 | 561,071 | Synthesis of nucleosides, antinomycins, etc., drug quality control. |
| 10. Health Insurance Plan of Greater New York, New York, N.Y. | 63-49 | 550,000 | Design and conduct of study on value of mammography in reducing breast cancer. |

UNIVERSITIES

| | | | |
|---|---|---|---|
| 1. Chicago Medical School, Chicago, Ill. | 65-67 | $1,154,389 | Carcinogenesis research and bioassays. |
| 2. Michigan State University, East Lansing, Mich. | 65-100 | 695,125 | Human/canine leukemic transmission trials; etiology of canine leukemia. |
| 3. Baylor University, Houston, Tex. | 63-590 | 576,325 | Research on viruses in human leukemia/lymphoma specimens. |
| 4. University of Texas, Houston, Tex. | 65-604 | 323,940 | EM, virological, tissue culture and immunofluorescence studies of human leukemia/lymphoma tissues; mycoplasma monitoring. |
| 5. University of Pennsylvania, Philadelphia. Pa. | 65-1013 | 310,748 | Research on experimental and natural transmission of bovine leukemia; EM tissue culture and related etiologic studies. |
| 6. University of Texas, Houston, Tex. | 66-1156 | 267,465 | Establish cancer pharmacology unit. |
| 7. University of St. Louis, St. Louis, Mo. | 67-692 | 265,101 | Genetic material in human cancers. |
| 8. University of California, Berkeley, Calif. | 65-609 | 256,563 | Bovine leukemia transmission studies. |
| 9. University of Michigan, Ann Arbor, Mich. | 65-639 | 219,918 | Research on virus particles in plasma-tissue culture specimens. |
| 10. George Washington University, Washington, D.C. | 64-515 | 195,230 | Investigations of virus-induced tumor antigens. |

INDIVIDUAL (NONE)

RADIATION RESEARCH

Mr. MICHEL. Did I read somewhere in the justifications that there is proposed a new research facility in your shop having to do with principally radiation?

Dr. ENDICOTT. We have two places where we are doing radiation work. One is at the Public Health Service hospital in Baltimore, and we have already put in a new machine there. The other is at the Clinical Center; for the most part we are still working with the equipment that was put in when the building was built and it is getting quite obsolete. So we are in the process of replacing the old outmoded equipment with new equipment.

Mr. MICHEL. Is that request for money in this budget?

Dr. ENDICOTT. I do not think so, sir.

Dr. SHANNON. If I could comment, these are not new facilities. This is the type of continuous updating that must go on with all high-

powered equipment. It just so happens that when you get into high-voltage radiation therapy machine, the cost is quite high. It is sufficiently high that each item is looked on as an individual item in relation to what it will do to a total program. When I shook my head that we were not planning new installations, it was in the sense that these are ongoing programs.

CONSTRUCTION OF RESEARCH FACILITIES

Mr. MICHEL. Would it be correct to say there is no construction money in your portion of the budget at all?

Dr. ENDICOTT. That is correct.

Mr. MICHEL. Absolutely none for construction?

Dr. ENDICOTT. I should qualify that though. It is contained within our contract authority.

There is an authority to use operational funds for the construction of specialized facilities that are required to carry out a particular project. But ther are no funds here for construction as such.

I think I found an item here "Specialized research centers," research centers for radiation therapy, pharmacology, and so on. They are not in-house; they are university-based centers.

Mr. MICHEL. Is it possible for a university to get a contract and to be carrying on some construction by way of this contract?

Dr. ENDICOTT. Yes, sir. But it is quite unusual.

Mr. MICHEL. If it is unusual, there would only be a few. So why do you not put in the record those institutions that are carrying on some form of construction by this means of a contract rather than having just open-faced construction of facilities?

Dr. ENDICOTT. Yes, sir. I can give you some specific examples.

One was at the University of Pennsylvania Veterinarian School to construct an isolation barn where we could study leukemia in cattle. A special barn.

Another place we built a similar kind of isolation facility for dogs, another one for cats.

Mr. MICHEL. On an item like that, would our animal disease laboratory out in Ames, Iowa, be doing anything in this very same area?

Dr. ENDICOTT. Yes, sir; I think they have there.

Mr. MICHEL. Any coordination between them?

Dr. ENDICOTT. Yes, sir. I think there is very good coordination with the Department of Agriculture.

Mr. MICHEL. I think that is all, Mr. Chairman.

Dr. ENDICOTT. Mr. Learmouth just whispered to me there is no construction in the contracts this year.

Mr. MICHEL. 1969?

Dr. ENDICOTT. In 1968 or 1969. But I have mentioned a few special facilities that have been built in the past. We have been very, very careful with this authority.

Mr. MICHEL. I would hope you would be.

In these subcommittees where we are overseeing the operation of the various departments, usually these construction items are blocked out and set out in specific line items so we can make sure that this thing does not get out of hand. Of course, there are devious ways of getting

construction without being open faced about it through contractual arrangements.

I just wanted to make sure we are not letting this thing get out of hand, and we do not resort to these backdoor approaches to construction. It seems to me once we get in this facilities business, we are in it for good.

That is all, Mr. Chairman.

Mr. FLOOD. Mr. Hull?

Mr. HULL. Thank you, Mr. Chairman.

## SMOKING AND HEALTH
## LUNG CANCER AND AGE DISTRIBUTION

Dr. Endicott, have there not been some studies which indicate that the age at which a person develops lung cancer is not affected by how much he has smoked during his lifetime?

Dr. ENDICOTT. I am afraid I do not know, sir.

Mr. HULL. In other words, does it appear that lung cancer tends to occur at about the same age in an individual who has been a heavy smoker or one who started smoking early in life as in an individual who smoked less or did not smoke at all?

Dr. ENDICOTT. So far as I am aware, and this is just a general impression, I have not looked into this as detailed as one should, but it is my general impression that the distribution of ages amongst those who die of lung cancer are about the same whether they are smokers or nonsmokers. I think that is probably true, but I have not studied it so that I can say so for sure.

Mr. HULL. Has the National Cancer Institute conducted any studies to determine whether the amount of or duration of smoking has any relationship to the age at which lung cancer occurs, and if so, what are the findings?

Dr. ENDICOTT. I would be happy to supply that for the record.

Mr. HULL. Fine.

(The information follows:)

### SMOKING RELATIONSHIP OF AGE TO LUNG CANCER

The National Cancer Institute in its studies of the effect of the amount and duration of smoking on lung cancer risks has used age-specific mortality rates to contrast the experience of nonsmokers with the various groups of cigarette smokers. Comparisons of age-specific mortality may be reduced into a summary index—a mortality ratio which expresses the mortality of cigarette smokers as a multiple of the risk for nonsmokers. The latest results from the Veterans' Administration study indicate the lung cancer mortality risk for all cigarette smokers to be 10.9 times that for nonsmokers.

Abelin has investigated the question of difference in average age of death between cigarette smokers and nonsmokers (Am. J. Epid.: 81, 254). Combining the data from the three major prospective studies conducted in the United States, he prepared life tables for regular cigarette smokers and nonsmokers. He found that the life expectation of regular cigarette smokers at age 40 was 5.1 years less than that for nonsmokers taking all causes of death into account. The difference in expectation of life in a life table population is another way of expressing the difference in average age of death.

Abelin did not compute the differences in life expectation attributable to lung cancer or other specific diseases. However, it is known that more than half of the overall difference of 5.1 years must be due to cardiovascular disease. An approximate computation carried out by the Biometry Branch of the National Cancer Institute indicates the deficit in life expectation among regular cigarette smokers ascribable to their higher lung cancer mortality was 1.2 years. This latter figure is consistent with the overall difference found by Abelin and can

be regarded as close to the result to be obtained through use of Abelin's more precise methods.

The fact that elevenfold higher lung cancer death rates among regular cigarette smokers results in such a small difference in the average age of lung cancer death for cigarette smokers and nonsmokers may at first glance seem surprising. The explanation is:

(*a*) Lung cancer is one of many competing causes of death and numerically far less important than cardiovascular disease. The relatively small number of deaths from lung cancer does not make a big contribution to the overall deficit in life expectation.

(*b*) Most lung cancer deaths occur between ages 40 and 75 among both smokers and nonsmokers and mortality from this cause rises with age in both groups. The higher risks among cigarette smokers did not deviate greatly from the age pattern noted for nonsmokers. The risks for smokers were transferred to a higher level without much change in the internal age relationships. Under these circumstances, only a small difference in average age of lung cancer deaths could be expected. Only when the shape of the lung cancer mortality curve by age is markedly displaced or otherwise changed (as may prove to be the case for uranium miners) could a pronounced shift in average age at death result.

Because the average age at death has been an insensitive and inadequate indicator of the magnitude of changes in lung cancer risks, the studies conducted by the National Cancer Institute have emphasized more direct comparisons based on age-specific evidence and mortality rates.

Mr. HULL. Is it not true that in the case of workers who have been exposed to radioactive materials or chemicals which cause lung cancer, that the age at which they develop lung cancers does appear to be related to the amount of exposure they have had to these materials; that is, the greater the exposure the earlier lung cancer occurs?

Dr. ENDICOTT. I could give you an impression, but I would rather check it and put it in the record.

Mr. HULL. If you will.

(The information follows:)

EXPOSURE TO RADIOACTIVE MATERIALS OR CHEMICALS IN RELATIONSHIP OF AGE TO LUNG CANCER

It is true that workers exposed to radioactive materials develop lung cancers at an earlier age, related quantitatively to the amount of exposure they have had to the radioactive materials. This is probably also true in the case of workers exposed to a chemical/industrial atmosphere, but the difficulty in quantitating man's exposure to chemicals makes this a qualified answer. Of course, in chemical carcinogenesis in animals, as exposure increases, the animals develop more tumors earlier.

Mr. HULL. If this is the case, is it correct to say that cigarette smoke does not seem to have the same characteristics as these industrial and occupational agents which have been identified as causes of lung cancer?

You can also put that in the record.

Dr. ENDICOTT. Yes.

(The information follows:)

CHARACTERISTICS OF CIGARETTE SMOKE VERSUS INDUSTRIAL AND OCCUPATIONAL AGENTS PERTAINING TO LUNG CANCER

Cigarette smoke, per se, being a complex mixture of substances, is not truly comparable to any single industrial/occupational agent, although it may be comparable to a given industrial/occupational environment or condition in which a variety of agents are present. In comparisons of cigarette smoke with industrial/occupational environments, striking similarities and differences are found. Carcinogens found in selected industrial/occupational conditions include polycyclic aromatic hydrocarbons (industries using or producing mineral oil, coal tar, waxes, asphalt, carbon black, or rubber), arsenic, chromium, nickel, beryllium

(mining and processing industries), asbestos, specific chemical compounds (the chemical industries), and radioactive elements (the uranium mines). Cigarette smoke contains representatives of several of these classes of carcinogenic agents in addition to other agents of unknown potential. Accordingly, some of the constituents of cigarette smoke have characteristics in common with constituents of industrial/occupational environments or conditions to which lung cancer has been linked.

In no case is the exposure of the cigarette smoker truly comparable to that received in any specific industry. While other constituents of cigarette smoke may have little or nothing in common with the constituents of industrial/occupational environments to which lung cancer has been linked, these constituents of cigarette smoke may facilitate cancer development (cocarcinogenesis). Compounds in the category of cocarcinogens include aliphatic hydrocarbons and phenols, both present in cigarette smoke.

CANCER CAUSATION

Mr. HULL. Last year in your prepared statement and in your testimony, you testified that the ultimate solution to the cancer problem is probably still locked in the cell.

Do you still feel the solution to the cancer problem is locked in the cell?

Dr. ENDICOTT. Yes, sir.

Mr. HULL. Do we know what causes cancer and its mechanism or do we only have theories that require further study and research?

Dr. ENDICOTT. The latter, sir.

Mr. HULL. Last year you testified that very little was known about the disease emphysema and its cause or causes. Is this still true?

Dr. ENDICOTT. Yes; it really is.

Mr. HULL. Last year in your testimony before this committee you indicated that it had not been scientifically established that cigarette smoking causes heart disease. Is that not still correct?

Dr. ENDICOTT. Yes, sir; I think it is.

Mr. HULL. Dr. Endicott, last year you filed for the record a joint report from the NCI and the Division of Environmental Health Sciences in regard to tobacco and health. This report was submitted in response to a question by Mr. Natcher inquiring if you had research which proved cigarette smoking caused lung cancer. The report filed begins:

The evidence suggesting a role for cigarette smoking in the causation of pulmonary diseases derives from three main areas of study.

Dr. Endicott, do you still agree there is a difference between medical proof and evidence suggesting a role?

Dr. ENDICOTT. Yes, sir; I certainly do.

Mr. HULL. Is not most of the evidence statistical?

Dr. ENDICOTT. No, sir; I would not say that that is so.

Mr. HULL. Neither you nor anyone else knows what causes cancer; is that not correct?

Dr. ENDICOTT. I would like to answer that in this way——

Mr. HULL. Is that not what continued research and study is all about?

Dr. ENDICOTT. Yes, sir. We do know a number of things which will cause cancer; but the thing which is so puzzling about it is how they act because they are so different. Radiation, chemicals, viruses. And we can prove that they cause cancer; but what is so hard to understand, and this we do not know, is how they do it. What is the mecha-

nism; how do these greatly different factors operate to bring about the same end result? And that we do not know, sir.

Mr. HULL. Dr. Endicott, have you yet determined anything in cigarette smoke that is the cause of illness and, if removed from the cigarette, would make a cigarette "safe"?

Dr. ENDICOTT. There are a number of substances which are capable of causing serious biological damage. They are, however, present in very small amounts usually, and taken alone not any one of them, we believe, is present in sufficiently high concentration to assign it the responsibility for the observed effects of smoking. Either we have missed a very powerful one and have failed to identify it or we are dealing here with a combined effect of a very complex mixture to which perhaps a dozen or two dozen different chemical substances are contributing.

It is almost certainly in this latter thing. I do not think we are going to suddenly find the thing. We are up against a very, very tough and difficult problem of a complex mixture.

Mr. HULL. Dr. Endicott, assuming cigarettes to be unsafe, which I do not accept, can the removal of some ingredients make them even less safe?

Dr. ENDICOTT. It is quite possible to make them worse; yes, sir.

ANTICARCINOGENS

Mr. HULL. What is an anticarcinogen?

Dr. ENDICOTT. The scientists use this term to refer to a substance which will counteract the effect of a chemical which causes cancer.

In other words, they have a system of using a known chemical carcinogen and add one more chemical to the mix and neutralize the cancer-causing effect.

Mr. HULL. Are there any anticarcinogens in cigarette smoke?

Dr. ENDICOTT. Yes, sir; I think there are.

Mr. HULL. Would you give us a summary on that for the record?

Dr. ENDICOTT. Yes, sir.

(The information follows:)

ANTICARCINOGENS IN CIGARETTE SMOKE

Anticarcinogens are those compounds which have in common an ability to inhibit the induction of cancer by other materials or compounds. The subject of anticarcinogenesis has received sporadic interest since Berenblum reported the experimental inhibition of tumor induction by mustard gas and other compounds in 1929, 1931, and 1935 (see references 1, 2, and 3). Other investigators (references 4 through 10) have since demonstrated inhibition of a potent carcinogen by a weak carcinogen. More recently, a broad spectrum of chemical agents have been shown to retard the rate of tumor induction. Kotin et al. (reference 11) have demonstrated anticarcinogenic properties in compounds related to carcinogens.

One of the more widely accepted explanations for anticarcinogenic action by compounds related to a carcinogen has been based on competition between the two compounds for a limited number of sites for action on the vulnerable cell. This phenomenon is comparable to that observed between vitamins and some of their closely related derivatives, termed antivitamins.

These observations "are particularly pertinent in attempting to assess the quantitative role of carcinogens present in polluted urban air and cigarette smoke in the pathogenesis of lung cancer" (reference 12).

The available evidence points to presence of anticarcinogens in cigarette smoke although the anticarcinogens have not been identified fully or characterized with

respect to significance, but the causal relationship between cigarette smoking and lung cancer mortality remains nonetheless.

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11. Kotin, P., et al: Inhibition of Effects of Some Carcinogens by their Partially Hydrogenated Derivatives, Science *123*: 102, 1956.
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TAR AND NICOTINE

Mr. HULL. Do you have any evidence, studies, or research reports, to indicate that the lower tar and nicotine content cigarettes are safer to smoke?

Dr. ENDICOTT. Yes, sir; there is some evidence to support that.

Mr. HULL. Would you place in the record at this point any research studies or reports you are aware of that indicate lower tar and nicotine content assures a safer cigarette?

Dr. ENDICOTT. Yes, sir.

(Information follows:)

RESEARCH STUDIES OR REPORTS THAT INDICATE LOWER TAR AND NICOTINE CONTENT ASSURES A SAFER CIGARETTE

In a recent study entitled, "Cancer of Lung Related to Smoking Behavior," [1] the author reported strong correlations between lung cancer experience and types of smoking behavior leading to excess exposure to tar and nicotine. Smoking behavior was characterized according to intensity and variation in puffing rates, and tar and nicotine production was determined by quantitating the tar and nicotine yields obtained when cigarettes were smoked imitatively on a smoking machine.

As the author states, the findings suggest means of reducing exposure to tar and nicotine by altering smoking behavior. The evidence presented is strong but,

[1] "Cancer of Lung Related to Smoking Behavior," by Saxon Graham, Cancer 21: 523, 1968.

as with all investigations in this field, additional studies should be undertaken to confirm the findings and observations. It appears reasonable to conclude, tentatively, from the author's observations that lower tar and nicotine cigarettes would be safer to smoke than "ordinary" or high tar and nicotine content cigarettes.

Mr. HULL. Do you still agree with the 1964 Surgeon General's Report that nicotine is not an important health hazard?

Dr. ENDICOTT. It is a hazard to a small group of individuals who have hereditary predisposition to a certain type of vascular disease. If you eliminate that group of people, I think it would be difficult to assign any known nicotine hazard.

Dr. SHANNON. Could I add to that answer and make it a little more limited, because there is no doubt that nicotine is very hazardous. The question here is does nicotine, in the amount taken in moderate smoking, cause identifiable disease. I think Dr. Endicott's answer is that—except for Buerger's disease which can be tied specifically to moderate smoking as one of the causes—there are no such conditions. I think any scientist would say that nicotine, as such, is a chemical substance that can produce dire harm to the body. It is a quantitative question here.

Mr. MICHEL. If you will yield.

Mr. HULL. Yes.

FEDERAL TRADE COMMISSION STUDY

Mr. MICHEL. Going back to the question before with respect to the amounts of resins and tars that might be found in any given brand of cigarettes, I recall the publication recently from the Federal Trade Commission evaluating cigarettes for their contents of one kind or another. At that time I was somewhat surprised because the first thing that came to my mind was, here was a Government agency taking it upon itself to be a consumer's guide. If they could do it for cigarettes, they could do it for automobiles or television sets or some such other thing.

To answer Mr. Hull's question, would you draw upon the evaluation made, for example, by the Federal Trade Commission to give him an answer, or would your answer be derived strictly from information you developed in your shop?

Dr. ENDICOTT. I had intended to include evidence wherever it came from, without regard to where or who supported it.

Mr. MICHEL. But with appropriate attribution of where that information came from?

Dr. ENDICOTT. Yes, sir; I intended to do that.

Mr. MICHEL. I would hope you would.

Dr. ENDICOTT. To include a bibliography.

Mr. MICHEL. I think too often on some of these highly technical matter, there are only a few individuals and institutions capable of rendering a valued judgment and it is sometimes the view of a very small number of people or one individual and cannot necessarily be taken as carte blanche authority that heaven has spoken and therefore there can be no dissent from that finding. Thank you.

EFFECT OF HEW REORGANIZATION ON NATIONAL CANCER INSTITUTE

Mr. HULL. Dr. Endicott, how will the HEW reorganization affect the National Cancer Institute?

Dr. SHANNON. Could I answer?

Mr. HULL. Yes.

Dr. SHANNON. The answer to that is that we do not know what the reorganization is going to be, sir.

Mr. HULL. Then you do not know about the present reorganization plans?

Dr. SHANNON. We do not, sir. That is under consideration at the present time and we do not know precisely what is being considered or the schedule for any changes.

FACTORS IN LUNG CANCER CAUSATION

Mr. HULL. Dr. Endicott, I asked the Surgeon General about his interest in the constitutional factor and he said some people were more susceptible than others to lung cancer. I am interested in whether or not there may be some influence at work which could account for lung cancer and also for its reported statistical association with smoking. What do you think about the possibility of some such third factor or influence?

Dr. ENDICOTT. I am convinced there are many factors at work here; and I have a strong suspicion, and it is only a suspicion, I have not the scientific evidence for it, that we are going to find a virus in this mess.

PHS REPORT ON SMOKING AND HEALTH

Mr. HULL. Dr. Endicott, the following statement appears in the PHS Report on Cigarette Smoking and Health Characteristics:

> Some third factor, possibly psychologic or biologic, is causing both the condition and the smoking habit.

This is stated to be one of the possibilities explaining statistical findings. Do you agree?

Dr. ENDICOTT. It is a possibility, yes, sir.

Mr. HULL. Is not most of the evidence said to link cigarette smoking to lung cancer statistical?

Dr. ENDICOTT. The studies in man are statistical. The studies in the laboratory, while having a statistical design, are not ordinarily referred to as statistical studies, but of course numbers of animals, weights of organs, are recorded and analyzed with statistical techniques.

CIGARETTE TESTING

Mr. HULL. Dr. Endicott, how do you plan to test various cigarettes?

Dr. ENDICOTT. We are working on that at the present time. We have not yet decided which tests to use. It will certainly be a multiple test approach, and I think probably most of the tests will be carried out both on material from the solid phase, tar, as well as the gaseous phase.

Mr. HULL. This will be your suggestion in this area then?

Dr. ENDICOTT. Yes, sir, but the specific tests we have not decided yet, which battery of tests to use. It is under very active discussion right now.

Mr. HULL. Are not the findings, reports, and gossip of the lung cancer task force going to be picked up and ballyhooed by various people, whether you are ready to make an announcement formally or not about some item you think is important?

Dr. ENDICOTT. It is a distinct possibility. I am hoping it will not happen.

Mr. HULL. Will there not likely be a lot more people crying "I found it" with regard to filters and claiming that cigarette companies should use their discovery?

Dr. ENDICOTT. Yes, sir; they are doing that already.

Mr. HULL. How will you prevent misuse of the task force of this sort?

Dr. ENDICOTT. I think we will be up against the same proposition one always is, the problem of trying to distinguish between those who have a legitimate claim for attention and those who are simply trying to use us. I expect we will have troubles here.

In my opinion it would be a mistake for us to operate behind a veil of secrecy, because the work, as it proceeds, the information is necessary for those who have an honest and sincere desire to move in the same direction as we want to move.

So I think we have to make our research findings available. And they could be used in all sorts of propaganda situations, and probably will.

Dr. SHANNON. Mr. Hull, I believe that if the Cancer Institute uses the same approach as they used in cancer chemotherapy and viruses related to cancer, this will largely be avoided. There will be official, periodic reports that have the concurrence of the guiding groups to indicate what things the task force believes warrant scientific consideration.

I think in the case of an area of such public interest and industry concern as cigarettes, it would be wise to have such reports actually in a numbered series. I think that approaching the formal release of information that way, at the time it is accumulated, will do much to prevent misuse of information that is too premature for serious consideration. This will do more to prevent that type of misuse of information than any other single thing and I am sure this will be done.

Dr. ENDICOTT. There is another problem area here, sir. This is the problem of how we should deal with trade secrets.

We have had to face this in our work with the pharmaceutical industry. It is a delicate and difficult problem area and there has to be give and take on both sides.

In the case of secret chemicals submitted to us by industry in the drug area, the compromise which we reached was that we would maintain the secret for a period of 1 year after we supplied them with our test results before we made both the chemical and the results public. I am sure there will be trade secrets in the highly competitive tobacco industry which will have to be dealt with in some manner, but we have not actually started discussions with the industry of this problem. And I cannot truthfully say I know what their attitude will be.

Mr. HULL. Dr. Endicott, will the clearinghouse and the task force on smoking and health, which I understand were formed to propagandize your findings, keep the secret along with the others?

Dr. ENDICOTT. The trade secret part of it will be secret, the only people who will know about it will be the people doing the tests and the company submitting the material for testing. A trade secret is a trade secret.

Mr. HULL. I know they are supposed to be, but it does not always come out that way.

Dr. SHANNON. May I comment on that?

We have had a tremendous experience, going back to 1902 with the establishment of the Biologics Control Act, in dealing with industry. Industrial processing and know-how, and such things as are appropriate to them and not to the public, have been held in confidence without any problem whatsoever.

We have been dealing in the field of cancer chemotherapy with information that relates to patentability of chemical compounds that may be very important therapeutic agents since about 1957. And in all of that experience with biologics control and with the cancer chemotherapy program, there has, to my knowledge, been no breach in this type of information.

During the war years, in the malaria chemotherapy program we had comparable relatonships with the entire pharmaceutical industry. This obtained over a period of 4 years during the war and about 3 or 4 years after, first by the Committee on Medical Research of the Office of Scientific Research and Development, and later by the National Institutes of Health.

There was no breach in secrecy there. So I feel very confident that reasonable arrangements can be made. The industrial groups have a very large experience with HEW, not only in NIH but also with the Food and Drug Administration. In a very real sense, I believe, they accept an agreement to restrict the availability of information at its face value. This does not trouble me at all, Mr. Hull.

INTRAMURAL ACTIVITIES

Mr. HULL. Dr. Endicott, I am not clear why you seem to want more people under your direct control rather than wanting to use grants and contracts. Why is this?

Dr. ENDICOTT. It is clear to me that the effort in the lung cancer area is going to be primarily carried out through contracts or grants, but it does take a number of people under my direction to manage such programs, particularly contract programs. The extent of surveillance and control in contracts is much greater than in grants and it takes more trained men to do it.

Mr. HULL. How big do you eventually expect your division to be?

Dr. ENDICOTT. We are limited to a very considerable extent by space. We are just finishing two new buildings. We will be moving a large number of our staff into those buildings and further expansion will be pretty much limited by those buildings. I would say——

Mr. HULL. Is that the only think holding you back from a larger organization?

Dr. ENDICOTT. That has been one of my great frustrations, sir.

This committee authorized the new cancer research building in 1960, appropriated planning funds for it in 1960, and appropriated funds for its construction in 1961, and it will be pretty close to 1969 before

I get into it. Now that is a long, long wait, and we have had to improvise in rented space and so on. It has been very unsatisfactory. I am wandering. But to come back to your question, there will be room in those facilities to add perhaps 200 to 300 people. But we are requesting funds in this budget to add but 25 for the lung cancer task force and 43 all told.

Dr. SHANNON. Could I extend that, Mr. Hull?

At the present time, the Cancer Institute finds itself in the unfortunate position of having staff scattered around a number of locations in Bethesda and occupying a laboratory building that was built and completed in 1938. Of the two buildings that Dr. Endicott refers to, one is a small virus isolation experimental building that will permit handling these very hot viruses we talked about some time ago.

The other is a combined laboratory and office building. As Dr. Endicott occupies that, he will move out of the old building that was built in 1938. This will be renovated which will take about a year. It will be largely occupied by Engineering Development, by Arthritis, and by Heart.

When Dr. Endicott talks about two new buildings, he is not talking about two new buildings that will require total staffing. The new buildings will permit him to bring together, in one site, a good deal of his scattered operations and provide a portion of the scientists with resources that are better suited to the modern task of research.

In general, we do not have any plan for a substantial increase in the size of the NIH operation beyond its present development. The present building program will provide a building for Child Health and Human Development; an adequate facility for the Cancer Institute to pull a number of its programs together; a modest expansion of administrative space; and the experimental isolation facilities I spoke about.

The staff of the Cancer Institute, during a 10-year period, will totally occupy that building. I think Dr. Endicott's figure of about 200 people is a reasonable one.

The increase in staff beyond that, if there is any, will relate more to such activities as are authorized by the Congress, more particularly by this committee, in relation to extramural programs in universities and in industry for special purposes that are defined and defended before this group.

### EFFECT OF REORGANIZATION ON ENVIRONMENTAL HEALTH SCIENCES

Mr. HULL. Thank you, Doctor. Dr. Endicott, how will the PHS reorganization affect your Division of Environmental Health Sciences?

Dr. ENDICOTT. I have not any idea. I am interested, I might say, but I do not know.

Dr. SHANNON. I can give you some light on that, sir.

Mr. HULL. I would like to have some light from some place.

Dr. SHANNON. In all of the discussions that relate to reorganization, principally with Mr. Gardner and subsequent to his leaving, the intent has been to maintain the Environmental Health Sciences Division within the NIH structure. That is its present position.

Dr. STEWART. May I say the reorganization that is under study

would not change the National Cancer Institute as an organizational entity nor the Division of Environmental Health Sciences, which is now in the NIH as an organizational entity itself.

HEW DEMAND FOR MEDICAL MANPOWER

Mr. HULL. Dr. Endicott, do you not feel that massive talent hunts by HEW divert doctors who might otherwise be available to take care of sick people?

Dr. ENDICOTT. Yes, sir; they do.

Dr. SHANNON. Mr. Hull, I cannot let that statement go by.

In the first place, on the average, somewhat more than 50 percent of our scientific staff are non-M.D., and in any expansion of the activity this would also obtain.

In the second place, I would say we do not have a massive talent hunt underway because we do not propose any substantial change in the size of the operation.

I think that curtailment of support for the scientists at work will probably result in their working less effectively, but not in less of them working in research or in science.

So I think curtailment of the budget will limit the capability of the scientists while, at the same time, not providing additional physicians for the delivery of health services.

Mr. HULL. Dr. Endicott, as the Federal Government becomes more and more the source of research money, do not scientists become more dependent on such funds?

Dr. SHANNON. They do indeed, sir.

Dr. ENDICOTT. Yes, sir.

Mr. HULL. Do you not suppose this makes them more cautious in disagreeing with any official and HEW policies?

Dr. ENDICOTT. It might affect some of them, sir, but they are the most independent lot I ever had anything to do with.

100-MILLIMETER CIGARETTES

Mr. HULL. Dr. Endicott, do you object to the marketing of 100-millimeter cigarettes and, if so, why?

Dr. ENDICOTT. Sometimes I buy them.

Mr. HULL. Pardon me?

Dr. ENDICOTT. Sometimes I buy them.

Mr. FLOOD. What does that mean? Does it mean you smoke them?

Dr. ENDICOTT. Yes, sometimes.

Mr. HULL. Dr. Endicott, are you interested in developing shorter cigarettes?

Dr. ENDICOTT. If I thought that was the way to solve the problem I would be, but frankly, I do not think that is the way to solve the problem because people seem to like to buy the long ones.

TAR AND NICOTINE

Mr. HULL. Or are you interested in low-tar-and-nicotine cigarettes, or what?

Dr. ENDICOTT. Sir, in our present state of knowledge, it is my judgment that moving in the direction of low tar and nicotine is moving

in the right direction, but the problem is more complex than that. I do not think it would be solved by that alone.

If I may expand on that a little bit, we have a complex mixture here and selective removal of certain things will probably turn out to be more effective than just the nonselective reduction of tar and nicotine.

Mr. HULL. Is it not just a guess that there may be some advantage to a cigarette with less tar and nicotine?

Dr. ENDICOTT. Yes, sir; I think that would be consistent with the total body of evidence, that less tar and nicotine is probably less hazardous.

Mr. HULL. Dr. Endicott, would you say evidence, if there is any, favoring low-tar-and-nicotine cigarettes is very strong?

You could put it in the record if you care to.

Dr. ENDICOTT. All right.

(See page 432.)

Mr. HULL. Dr. Endicott, would you say it has been demonstrated beyond doubt that increased tar and nicotine means increased hazards?

Dr. ENDICOTT. Yes, I think there is evidence in that direction.

Dr. SHANNON. Mr. Hull, I think that series of questions may warrant some clarification. There is emphasis on tars because this is the fraction of the smoke that contains the mixture of material that can be shown to have certain biological properties that are presumed to be related either to the production of lung cancer or to the triggering of precancerous condition.

Mr. HULL. The reason I asked this question was to determine the present state of knowledge about so-called safer cigarettes.

Dr. ENDICOTT. If you can reduce the ones that carry the hazardous substances, the inference is you likely have improved the cigarettes, but there is no direct proof this is the case.

That is my opinion, that is an experimental inference rather than rigid proof that a specific thing has been accomplished.

Mr. HULL. I believe that is all, Mr. Chairman.

Thank you very much, Dr. Endicott, and you, Dr. Shannon.

Mr. FLOOD. Thank you, gentlemen.

JUSTIFICATION MATERIAL

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $183,356,000 | $187,707,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 25 | Research | | $81,656,000 | | $84,752,000 | | +$3,096,000 |
| | General research support grants | | (6,899,000) | | (6,838,000) | | (-61,000) |
| | Scientific evaluation grants | | (151,000) | | (151,000) | | --- |
| | Specialized research centers | | (12,590,000) | | (13,310,000) | | (+720,000) |
| | Leukemia research support centers | | (1,500,000) | | (1,500,000) | | --- |
| [illegible] | Fellowships | | 4,326,000 | | 4,422,000 | | +96,000 |
| [illegible] | Training | | 11,350,000 | | 11,641,000 | | +291,000 |
| | Direct operations: | | | | | | |
| 3 | Laboratory and clinical research | 498 | 16,032,000 | 512 | 16,533,000 | +14 | +501,000 |
| 35 | Collaborative research and development | 724 | 63,077,000 | 749 | 65,111,000 | +25 | +2,034,000 |
| .7 | Biometry, epidemiology, and field studies | 112 | 1,415,000 | 112 | 1,435,000 | -- | +20,000 |
| [illegible] | Review and approval of grants | 111 | 2,542,000 | 113 | 2,520,000 | +2 | -22,000 |
| [illegible] | Program direction | 56 | 1,316,000 | 58 | 1,293,000 | +2 | -23,000 |
| | Total obligations | 1501 | 181,714,000 | 1544 | 187,707,000 | +43 | +5,993,000 |
| | Unobligated balance, reserve | 42 | 1,642,000 | -- | --- | -42 | -1,642,000 |
| | Total, obligations and reserve | 1543 | 183,356,000 | 1544 | 187,707,000 | +1 | +4,351,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| PUBLIC HEALTH SERVICE | | | |
| Total number of permanent positions..... | 1,419 | 1,462 | +43 |
| Full-time equivalent of all other positions..... | 30 | 30 | -- |
| Average number of all employees..... | 1,432 | 1,460 | +28 |
| Personnel compensation: | | | |
| Permanent positions..... | $13,277,000 | $13,901,000 | +$624,000 |
| Positions other than permanent..... | 162,000 | 163,000 | +1,000 |
| Other personnel compensation..... | 114,000 | 114,000 | --- |
| Total personnel compensation..... | 13,553,000 | 14,178,000 | +625,000 |
| Personnel benefits..... | 1,589,000 | 1,640,000 | +51,000 |
| Travel and transportation of persons.... | 626,000 | 726,000 | +100,000 |
| Transportation of things..... | 106,000 | 106,000 | --- |
| Rent, communications, and utilities..... | 422,000 | 422,000 | --- |
| Printing and reproduction..... | 404,000 | 404,000 | --- |
| Other services..... | 1,287,000 | 1,487,000 | +200,000 |
| Project contracts..... | 50,777,000 | 51,843,000 | +1,066,000 |
| Payment to "National Institutes of Health management fund"..... | 9,607,000 | 9,708,000 | +101,000 |
| Supplies and materials..... | 2,991,000 | 3,350,000 | +359,000 |
| Equipment..... | 2,000,000 | 2,000,000 | --- |
| Grants, subsidies and contributions..... | 97,332,000 | 100,815,000 | +3,483,000 |
| Subtotal..... | 180,694,000 | 186,679,000 | +5,985,000 |
| Deduct quarters and subsistence charges. | -10,000 | -10,000 | --- |
| Total, Public Health Service..... | 180,684,000 | 186,669,000 | +5,985,000 |

Obligations by Object--continued

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| ALLOCATION TO VETERANS ADMINISTRATION | | | |
| Total number of permanent positions..... | 82 | 82 | -- |
| Full-time equivalent of all other positions..... | 10 | 10 | -- |
| Average number of all employees..... | 86 | 86 | -- |
| Personnel compensation: | | | |
| Permanent positions..... | $596,000 | $602,000 | +$6,000 |
| Positions other than permanent..... | 155,000 | 156,000 | +1,000 |
| Other personnel compensation..... | 1,000 | 1,000 | --- |
| Total personnel compensation..... | 752,000 | 759,000 | +7,000 |
| Personnel benefits..... | 54,000 | 55,000 | +1,000 |
| Travel and transportation of persons.... | 71,000 | 71,000 | --- |
| Transportation of things..... | 1,000 | 1,000 | --- |
| Rent, communication, and utilities..... | 1,000 | 1,000 | --- |
| Other services..... | 30,000 | 30,000 | --- |
| Supplies and materials..... | 54,000 | 54,000 | --- |
| Equipment..... | 67,000 | 67,000 | --- |
| Total, Veterans Administration..... | 1,030,000 | 1,038,000 | +8,000 |
| Total obligations by object..... | 181,714,000 | 187,707,000 | +5,993,000 |

## Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $183,356,000 |
| Unobligated balance, reserve | -1,642,000 |
| 1968 total estimated obligations | 181,714,000 |
| 1969 estimated obligations | 187,707,000 |
| Total change | +5,993,000 |

| Increases | Base Positions | Base Amount | Change from Base Positions | Change from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. One extra day of pay, in 1969 | --- | --- | --- | +$19,000 |
| 2. Annualization of 1968 pay raise costs | --- | --- | --- | +220,000 |
| Subtotal, built-in increases | --- | --- | --- | +239,000 |
| B. Program | | | | |
| 1. Research grants | --- | $81,656,000 | --- | +$3,096,000 |
| 2. Fellowships | --- | 4,326,000 | --- | +96,000 |
| 3. Training | --- | 11,350,000 | --- | +291,000 |
| 4. Laboratory and clinical research | 498 | 9,063,000 | 14 | +200,000 |
| 5. Collaborative research and development | 724 | 62,002,000 | 25 | +1,900,000 |
| 6. Review and approval of grants | 111 | 1,493,000 | 2 | +25,000 |
| 7. Program direction | 56 | 969,000 | 2 | +45,000 |
| Subtotal, program increases | --- | --- | 43 | +5,653,000 |

| Increases | Base Positions | Base Amount | Change from Base Positions | Change from Base Amount |
|---|---|---|---|---|
| C. Payment to "National Institutes of Health Management fund" for centrally furnished services: | | | | |
| 1. Laboratory and clinical research.. | --- | $6,969,000 | --- | +$224,000 |
| 2. Collaborative research and development..... | --- | 1,075,000 | --- | +18,000 |
| 3. Biometry, epidemiology, and field studies..... | --- | 167,000 | --- | +2,000 |
| 4. Review and approval of grants..... | --- | 1,049,000 | --- | -65,000 |
| 5. Program direction... | --- | 347,000 | --- | -78,000 |
| Subtotal, management fund increases..... | --- | --- | --- | +101,000 |
| Total net changes requested. | --- | --- | +43 | +5,993,000 |

Explanation of Changes

Research grants--The program increase of $3,096,000 will provide an additional $2,437,000 for regular program grants and an increase of $720,000 for specialized research centers, offset by a decrease of $61,000 in general research support grants.

Fellowships--The program increase of $96,000 will provide $30,000 for postdoctoral fellowships, $30,000 for special fellowships, and $36,000 for research career development awards.

Training--The program increase of $291,000 will provide $98,000 for the graduate program and $193,000 for the cancer clinical training program.

Laboratory and clinical research--The program increase of $200,000 is requested for support of 14 new positions which will allow increased research in the areas of biology, endocrinology, immunology, metabolism, and surgery.

Collaborative research and development--The program increase of $1,900,000 is requested for support of 25 new positions and expanded contract programs for the NCI task forces, mainly those for breast cancer and lung cancer. This is the first year that funds have been budgeted for the Lung Cancer Task Force.

Review and approval of grants--The program increase of $25,000 is requested for support of 2 new positions which are needed in relation to the expanded field of immunology.

Program direction--The program increase of $45,000 is requested for support of 2 new positions in order to increase operations research and systems communication aspects of the program planning activity.

## Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301-Research and Investigation, in general..... | Indefinite |
| Title IV, Part A--National Cancer Institute..... | Indefinite |

PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justification under the tab, "Preamble Paragraph" in Volume IV.

The Public Health Service Act, Title IV, National Research Institutes, Part A, National Cancer Institute--

"Sec. 401. The National Cancer Institute shall be a division in the National Institutes of Health."

"Sec. 402. In carrying out the purposes of section 301 with respect to cancer, the Surgeon General, through the National Cancer Institute and in cooperation with the National Cancer Advisory Council, shall--

(a) conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of cancer;

(c) Provide training and instruction in technical matters relating to the diagnosis and treatment of cancer;

(d) Provide fellowships in the Institute from funds appropriated or donated for such purpose;"

National Cancer Institute

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 1,501 | $15,142,000 | 1,544 | $15,818,000 | +43 | +$676,000 |
| Other expenses..... | --- | 166,572,000 | --- | 171,889,000 | --- | +5,317,000 |
| Total..... | 1,501 | 181,714,000 | 1,544 | 187,707,000 | +43 | +5,993,000 |

General Statement

The National Cancer Institute conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling cancer in man. These objectives are pursued directly through universities, non-profit research organizations and commercial concerns supported with grants and contracts and include both laboratory and clinical studies.

The overall 1969 increase requested for the National Cancer Institute totals $5,993,000. This amount includes $5,653,000 for program increases; $239,000 for mandatory increases of annualization of the 1968 pay raise and one extra day of pay in 1969; and $101,000 for payment to the NIH Management Fund for centrally furnished services.

There is a program increase of $3,096,000 in Research grants. This will allow small increases throughout the grant program including research in cancer causation, tumor growth, host-tumor relationship, epidemiology, diagnosis, therapy as well as basic research. The increase will also allow the establishment of an additional cancer research center located in a geographical area not now serviced by any existing faciltiy.

There is a program increase in Fellowship grants of $96,000 which will allow for modest cost-of-living increases. Emphasis will continue to be given to providing coverage in the shortage areas of radiation therapy, surgery, hematology, and clinical pharmacology.

There is a program increase in Training grants of $291,000 which will provide for the continuation of ongoing programs of graduate and cancer clinical training as well as allow for cost-of-living increases.

The direct operations portion of the budget allows for modest program increases of $200,000 under Laboratory and clinical research; $25,000 under Review and approval of grants; and $45,000 under Program direction. The largest increase within direct operations is in the area of Collaborative research and development. This includes a program increase of $1,900,000 for the NCI task forces, mainly Breast Cancer and Lung Cancer. The Lung Cancer Task Force funds will be used for new research efforts, to identify and reduce the hazardous components in tobacco and also to investigate other industrial-atmospheric-occupational factors and finally, to improve methods of detection, diagnosis, and treatment of lung cancer.

Research Grants

| | 1968 estimate | 1969 estimate | Increase or Decrease |
|---|---|---|---|
| Research projects..... | $60,516,000 | $62,953,000 | +$2,437,000 |
| Special programs..... | 21,140,000 | 21,799,000 | +659,000 |
| Total research grants.. | 81,656,000 | 84,752,000 | +3,096,000 |

Introduction

The National Cancer Institute, through its research grant program, stimulates and supports research activities in the broad areas of causation, nature, diagnosis, treatment, prevention and control of cancer. Research projects are conducted by investigators or groups of investigators at colleges, universities, hospitals, research institutions, and various other non-profit institutions. These programs cover a broad spectrum of activity ranging from those projects having single objectives to those which are broadly-based and cover multi-disciplinary areas, some involving the coordination and direction of the efforts of many investigators.

Program Plans in 1968 and 1969

Emphasis is being placed on basic and applied research and covers such areas as radiation, chemical carcinogenesis, immunology, drug development, virology, and epidemiology. There will be continued study of a variety of cancers in laboratory animals and in human patients. Investigations will also aim at the identification of cancer producing agents in the total environment. Demographic studies will continue with the aim of isolating these environmental factors in relation to specific types of cancer.

Additional studies will be conducted in the techniques of therapy, such as the effects of drugs and radiation in controlling the growth and spread of cancerous cells in living organisms. Since cancer is primarily a cell disease it is more imperative that increased emphasis be placed on carcinogenesis, cell biology, and clinical research studies. Support will continue in the clinical investigation of new anticancer drugs in approximately 125 institutions in the country. The investigators at these institutions are organized in seven cooperating groups, and their efforts are closely coordinated with the NCI program of procurement and development of anticancer drugs. In addition NCI will continue to explore other therapeutic modalities such as surgery, radiation, and immunology. Furthermore, the Institute will continue to support investigations involving the evaluation and development of the complex techniques needed to protect the leukemia patient from infection, a major cause of death in leukemia patients. Techniques now being studied include the use of sterile plastic tents or laminar-flow rooms which provide a germ-free environment for the patient and the essential supporting dietary nursing and other services. Also, investigations at approximately 30 leukemia research centers will be continued and will include the procurement, preparation, preservation, and administration of platelet transfusions to children with leukemia, and the evaluation of such transfusions in the prevention and treatment of hemorrhage, another major cause of death in leukemia patients.

The NCI currently supports 25 Specialized Research Centers which are performing intensive, highly specialized clinical research or laboratory research relating to prevention, diagnosis and treatment of cancer in man. These centers are organized on a single or multi-disciplinary basis which enables investigators in key disciplines to assist each other in developing and testing new principles and methods essential to the effective diagnosis and treatment of cancer. The emphasis of these centers is continually changing as new developments take place in cancer research and therapy. Early investigations related primarily to chemotherapeutic trials, but since that time have expanded to include host-defense mechanisms, the effect of cytotoxic drugs on immune responses, and the attempts to define more precisely the mechanism of the action of other anticancer agents. The role which man's environment plays, as related to his susceptibility to malignant disease from non-viral carcinogenic agents, will continue to be studied with particular emphasis on prevention. Studies of radiation biology, radiation, physics, and nuclear medicine are expanding. Emphasis will continue to be given to determining the optimum methods of employing chemotherapeutic drugs and other forms of therapy and to the use of radiation as an adjuvant to surgery and chemotherapy. Grants are also used to aid institutions in the development of long-range plans for cancer research, training, and clinical services, the development of specialized equipment and resources, the evaluation of the status and progress of cancer activities, and the establishment of new centers.

The $45,477,000 in 1969 designated for support of non-competing continuation projects contains an increase of $2,437,000 over the 1968 level of support. The following areas of program interest will continue to receive priority: (1) the factors relating to man's susceptibility to neoplastic disease (2) research related to experimental radiobiology and radiation therapy and their appropriate tools and techniques (3) the roles played in causation of malignancies by viruses (4) development and procurement of anticancer drugs and (5) studies in the provision of germ-free environment for the patient and the requisite dietary and nursing services.

The specialized research centers program will continue to support studies in radiation therapy, toxicology, pharmacology, and epidemiology, at approximately the same level as in 1968. The increase of $720,000 will allow for initial costs of one new center oriented toward radiation. Attempts will be made to locate the center in a geographical area not now serviced by any existing radiation facility.

The leukemia research support centers are expected to continue at the same level in 1969 as 1968. Emphasis will still be placed upon accumulating evidence regarding platelet replacement therapy and its use as an effective device in connection with the use of control drugs.

Research Grants Program Analysis

| Fields | 1968 estimate | 1969 estimate | Increase or Decrease |
|---|---|---|---|
| Cancer causation..... | $13,556,000 | $14,101,000 | +$545,000 |
| Tumor growth..... | 12,769,000 | 13,283,000 | +514,000 |
| Host-tumor relationship..... | 2,965,000 | 3,085,000 | +120,000 |
| Epidemiology..... | 1,210,000 | 1,259,000 | +49,000 |
| Diagnosis..... | 1,089,000 | 1,133,000 | +44,000 |
| Therapy..... | 17,429,000 | 18,131,000 | +702,000 |
| Basic research and other*... | 11,498,000 | 11,961,000 | +463,000 |
| Subtotal regular program.. | 60,516,000 | 62,953,000 | +2,437,000 |
| General research support grants..... | 6,899,000 | 6,838,000 | -61,000 |
| Scientific evaluation grants | 151,000 | 151,000 | --- |
| Specialized research centers | 12,590,000 | 13,310,000 | +720,000 |
| Leukemia research support centers..... | 1,500,000 | 1,500,000 | --- |
| Total research grants..... | 81,656,000 | 84,752,000 | +3,096,000 |

*Includes Sloan-Kettering single instrument grant

Distribution of Research Grants

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Noncompeting continuations..... | 896 | $43,040,000 | 880 | $45,477,000 | -16 | +$2,437,000 |
| Competing projects.. | 322 | 14,822,000 | 325 | 15,187,000 | +3 | +365,000 |
| Supplementals..... | (265) | 2,654,000 | (229) | 2,289,000 | (-36) | -365,000 |
| Subtotal Regular program..... | 1218 | 60,516,000 | 1205 | 62,953,000 | -13 | +2,437,000 |
| General research support..... | | 6,899,000 | | 6,838,000 | | -61,000 |
| Scientific evaluation..... | | 151,000 | | 151,000 | | --- |
| Specialized research centers..... | | 12,590,000 | | 13,310,000 | | +720,000 |
| Leukemia research support centers... | | 1,500,000 | | 1,500,000 | | --- |
| Total research grants..... | | 81,656,000 | | 84,752,000 | | +3,096,000 |

Fellowships

| | 1968 estimate | 1969 estimate | Increase or Decrease |
|---|---|---|---|
| Total fellowships..... | $4,326,000 | $4,422,000 | +$96,000 |

Introduction

Several kinds of awards designed to meet particular objectives are granted under this program. The program provides research training to individuals whose career development extends from the immediate postdoctoral period through the advanced stages of scientific attainment. Postdoctoral awards are made to qualified individuals with doctoral degrees and up to three years of relevant research experience. Special fellowships are for those who have had at least three years of postdoctoral research or professional experience, or who have completed at least three years of residency training in a clinical specialty. Special fellowships may also be awarded to senior investigators who wish to undertake additional training.

This budget activity also supports two other types of awards made to institutions for the purpose of fostering the development of young scientists with outstanding research potential for careers of independent research in disciplines related to cancer research. The research career development awards support young and promising investigators who require 5 to 8 years additional experience in order to improve their research skills and to develop a capability for independent investigation. Research career awards were made to established investigators of high quality for additional periods of their research careers. A prime goal of these programs is to produce researchers who can also train others to conduct research.

Program Plans in 1968 and 1969

In 1968 the number of awards in both the Postdoctoral and Special categories will increase substantially due to the rapidly expanding area of biochemistry, especially medicinal and organic chemistry as well as biophysical chemistry, Continued emphasis will also be given encouraging interest and increasing training in the critical shortage areas of radiation therapy, surgery, hematology, and clinical pharmacology.

In 1969 the Institute plans to continue support of the fellowships programs at approximately the same level as 1968. As in 1968, emphasis will continue to be given to providing coverage of the shortage areas of radiation therapy, surgery, hematology and clinical pharmacology. The 1968 increase of $96,000, coupled with an overall net decrease of three awards, will allow for modest cost-of-living increases.

Distribution of Fellowships

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Continuations | | | | | | |
| Noncompeting..... | 118 | $2,157,000 | 147 | $2,657,000 | +29 | +$500,000 |
| Competing..... | 56 | 717,000 | 66 | 845,000 | +10 | +128,000 |
| Supplementals..... | --- | --- | --- | --- | --- | --- |
| New awards..... | 155 | 1,452,000 | 113 | 920,000 | -42 | -532,000 |
| Total fellowships... | 329 | 4,326,000 | 326 | 4,422,000 | -3 | +96,000 |

Fellowships (By type of program)

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Postdoctoral..... | 115 | $921,000 | 111 | $951,000 | -4 | +$30,000 |
| Special..... | 89 | 1,075,000 | 88 | 1,105,000 | -1 | +30,000 |
| Research career | | | | | | |
| Career..... | 13 | 347,000 | 13 | 347,000 | --- | --- |
| Development..... | 112 | 1,983,000 | 114 | 2,019,000 | +2 | +36,000 |
| Total fellowships. | 329 | 4,326,000 | 326 | 4,422,000 | -3 | +96,000 |

Training Grants

| | 1968 estimate | 1969 estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants..... | $11,350,000 | $11,641,000 | +$291,000 |

Introduction

The National Cancer Institute provides grants to institutions for graduate research training for the purpose of insuring a continuous, ample reserve of qualified research personnel, and to relieve the critical shortages of professional manpower in specific areas concerned with research, teaching, and service. These grants may provide stipends for those in training in the various fields related to cancer research and underwrite expenses for equipment, supplies, and training staff. Through the clinical cancer training grants program, the National Cancer Institute aims to: (1) upgrade the quality of cancer instruction offered to graduate and undergraduate medical and dental students, and to interns, residents, clinical fellows, practitioners, and scientists; (2) broaden the scope and content of current cancer teaching; and (3) undertake innovations in methodology for teaching the clinical and public health aspects of comprehensive cancer management. These grants are provided to qualified institutions to expand and advance training in the prevention, diagnosis, treatment, rehabilitation, and public health aspects of cancer.

Program Plans in 1968 and 1969

During the current year, 193 programs will be supported. Continued emphasis will be given to training in radiation therapy and related basic disciplines. Emphasis will also be placed on establishing additional programs of clinical research training and conventional graduate programs in disciplines where cancer researchers are in short supply. Programming efforts will be intensified in: (1) radiotherapy, (2) clinical pharmacology, (3) chemical carcinogenesis, and (4) training related to regional medical programs.

Because of increased cost in such areas as personnel, equipment, and stipends, the increase of $291,000 in training grants for 1969 will provide for the continuation of ongoing programs, funding of selected high priority renewal grants on a constricted level, and the initiation of 3 new grants.

Distribution of Training Grants

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Continuations | | | | | | |
| Noncompeting..... | 165 | $9,440,000 | 144 | $8,643,000 | -21 | -$797,000 |
| Competing..... | 16 | 1,065,000 | 43 | 2,755,000 | +27 | +1,690,000 |
| Supplementals..... | (4) | 139,000 | (2) | 50,000 | (-2) | -89,000 |
| New programs..... | 12 | 706,000 | 3 | 193,000 | -9 | -513,000 |
| Total training grants | 193 | 11,350,000 | 190 | 11,641,000 | -3 | +291,000 |

Training Grants (By Program)

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Graduate..... | 94 | $5,880,000 | 93 | $5,978,000 | -1 | +$98,000 |
| Cancer clinical training | 99 | 5,470,000 | 97 | 5,663,000 | -2 | +193,000 |
| Total training grants | 193 | 11,350,000 | 190 | 11,641,000 | -3 | +291,000 |

Laboratory and Clinical Research

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 498 | $5,301,000 | 512 | $5,560,000 | +14 | +$259,000 |
| Other expenses..... | --- | 10,731,000 | --- | 10,973,000 | --- | +242,000 |
| Total..... | 498 | 16,032,000 | 512 | 16,533,000 | +14 | +501,000 |

Introduction

The research within this activity is designed to provide a basic understanding of cancer - how and why a cancer develops and grows, its effect on the host and the hosts effect on it, genetic influences, body defense mechanisms and how cancers differ from each other. The research embraces both laboratory and clinical research including surgical studies in animals and man. Biochemists, physiologists, biologists, and pathologists bring their special talents to bear on these complex problems. Out of such research in our laboratories and similar research in universities and cancer institutes has emerged the knowledge which has provided the basis for more applied programs in therapy and causation which are now moving so rapidly.

Program Plans in 1968 and 1969

The role of immunity in both cause and control of cancer receives increasing attention. Evidence of immunity to tumors caused by viruses has been demonstrated in animals and is being sought in man. The identification of tumor-producing viruses, or immunologic specificity of tumors in man, presumably would have applicability in therapy. Specific antibodies which combine with specific chemicals of known small molecular structure have recently been discovered. Knowledge of such chemical unions is sought because of possibilities of synthesizing specific antibodies against specific tumors in order to eliminate the cancer.

Cancer stems from a failure of the body to properly regulate cell growth. Cell regulatory systems are studied both at cellular and tissue levels. The finding of extra-nuclear DNA, heretofore thought to be only in the nucleus, has opened up entirely new approaches to the study of cell regulation which are pursued in NCI laboratories. Applicability of research on cell regulation to clinical cancer is found, for example, in hormone dependent tumors, such as some breast cancers, where the induction and control of tumor growth is significantly modified by steroid and protein hormones, even though such tumors may stem from other causes.

New information on kinetics of growth of tumor cell populations has generated new concepts on utilizing existing chemotherapeutic drugs in new dose schedules to enhance therapeutic benefit. These concepts have been tested and confirmed in actual use in treatment of a cancer known as mycosis fungoides. Successful application of these principles to the treatment of other cancers is expected.

No major shifts in areas of research emphasis are expected in 1969, although within these areas one finds constant change. There will be an enhanced effort in the field of tumor immunology and research on cell control systems, and new efforts will be initiated in the area of organ transplantation and research in developmental biology.

Today's progress in successful transplantation of whole organs in man encourages further exploration into feasibility of utilizing such transplant procedures in cancer surgery. Research designed to test transplant feasibilities has been initiated in primates and will be more fully studied in these laboratory animals prior to any practical utilization in the human.

Techniques found most useful to date in studying inductive systems in embryonic development are being applied to similar induction systems in the adult organism, both normally and in neoplastic transformation. The projected budget includes a modest increase in support of these efforts. Efforts directed toward bringing appropriately trained scientists into this area will be exerted according to the success of ongoing research and its promise for gain.

The program increase of $200,000 and 14 positions for 1969 will permit increased effort in areas noted above and continuation of other ongoing research efforts in the programs of biology, endocrinology, immunology, metabolism, and surgery.

An increase of $69,000 is requested for annualization of 1968 pay raise and $8,000 for an extra day of pay in 1969. There is also an increase of $224,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Collaborative Research and Development

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 724 | $6,959,000 | 749 | $7,290,000 | +25 | +$331,000 |
| Other expenses | --- | 56,118,000 | --- | 57,821,000 | --- | +1,703,000 |
| Total | 724 | 63,077,000 | 749 | 65,111,000 | +25 | +2,034,000 |

Introduction

The programs under Collaborative Research and Development are national efforts utilizing the contract research mechanism as well as investigations carried on directly in institute laboratories, to concentrate on major problems relevant to cancer. The research projects within the programs under this activity are interrelated, and changes in emphasis or major developments may cause a number of changes in many projects as their contributions of progress toward program goals are evaluated.

The National Cancer Institute established the Etiology and Cancer Therapy areas under this activity to provide strong central leadership and responsibility for carefully planned research activities. The etiology programs are focused on causes of cancer, the patterns of cancer occurrence, and their prevention. The therapy programs are concerned with finding the method of treating cancer through drugs and radiation. The addition of the line item, "Cancer Task Forces" is new to the budget in 1969 and brings together into one area the NCI task forces, notably, the Breast Cancer Task Force and the newly established Lung Cancer Task Force. Programs generated from task force activities will tend to cut across organizational lines and depend on a variety of ongoing activities within the Institute.

The following table indicates level of support by these major program areas:

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Etiology | 268 | $30,632,000 | 268 | $30,675,000 | --- | +$43,000 |
| Cancer Therapy | 390 | 27,069,000 | 390 | 27,136,000 | --- | +67,000 |
| Task Forces | 12 | 2,805,000 | 37 | 4,707,000 | +25 | +1,902,000 |
| Supporting Services | 54 | 1,496,000 | 54 | 1,500,000 | --- | +4,000 |
| National Institutes of Health Management Fund | --- | 1,075,000 | --- | 1,093,000 | --- | +18,000 |
| Total Collaborative Research and Development | 724 | 63,077,000 | 749 | 65,111,000 | +25 | +2,034,000 |

Etiology

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Total | 268 | $30,632,000 | 268 | $30,675,000 | --- | +$43,000 |
| Office of the Scientific Director | 26 | 806,000 | 26 | 807,000 | --- | +1,000 |
| Solid Tumor-Virus | 89 | 1,590,000 | 89 | 1,609,000 | --- | +19,000 |
| Contracts | --- | 3,384,000 | --- | 3,385,000 | --- | +1,000 |
| Carcinogenesis | 103 | 1,583,000 | 103 | 1,598,000 | --- | +15,000 |
| Contracts | --- | 6,195,000 | --- | 6,196,000 | --- | +1,000 |
| Demography Contracts | --- | 1,850,000 | --- | 1,851,000 | --- | +1,000 |
| Special Virus Leukemia | 50 | 727,000 | 50 | 732,000 | --- | +5,000 |
| Contracts | --- | 14,497,000 | --- | 14,497,000 | --- | --- |

Introduction

The Etiology area is charged with responsibility for the major share of the Institute's programmed research on cancer causation and prevention, including the major portion of the Special Virus Leukemia program. Its investigations extend from the studies of cancer induction in defined human and animal populations to studies under laboratory conditions of the fundamental aspects of the mechanisms by which viral and chemical agents produce cancers by altering the metabolism in living systems. Scientists are responsible not only for their individual research, but also for provision of strong central leadership in the conceptualization, design, and implementation of an imaginative and integrated attack upon these problems, in collaboration with other investigators in this country and abroad.

Central to the Etiology area's approach is the concept of an interaction of multiple causative factors contributed by man as a host and by his environment. The Demography programs (further described under "Biometry, epidemiology and field studies") in addition to providing a continuous monitoring of cancer incidence, prevalence, and mortality rates and trends, are designed to analyze defined populations having unusual risks to specific cancers or known exposure to high risk environments, to reveal statistically significant cause-and-effect associations and dissociations leading to the discovery of etiologic factors and agents. The experimentally oriented units of the Etiology area select and combine, under carefully controlled conditions, those host and environmental factors which appear to be significant in cancer etiology. From this point, they proceed to verify or deny such significance by success or failure in producing cancer in animals. It may then be seen that the synthetic approach on one hand and the analytic approach on the other are purposely united in the Etiology area to complement one another.

## Program Plans in 1968 and 1969

### Carcinogenesis

The Carcinogenesis Studies area is concerned with cancer causation by chemical agents with respect to advancing understanding of mechanisms of cancer induction, improving techniques for detecting and identifying those factors in man's environment causing or contributing to cancer, and identifying cancer-causing agents. Research efforts are in large measure based upon leads provided by epidemiological studies and clinical observations in the areas of occupational and environmental cancer.

The organization continues to direct a broad program of collaborative research which places greatest emphasis upon the elucidation of those environmental agents which may constitute a carcinogenic hazard for large segments of the human population. Research contracts initiated and implemented by the Carcinogenesis area are providing essential information on potentially carcinogenic materials, and support studies on the role of multiple physical, chemical, and biological factors in cancer induction. Data obtained in the program are making significant contributions to an understanding of the roles of pesticides, tobacco, smoke components, fungal toxins, and other agents of known or suspected carcinogenic activity which are of intense interest to commerce and the general public.

In-house and cooperative studies that endeavor to clarify the interaction of carcinogenic agents with living systems at the host, tissue, cellular, and molecular levels are progressing well. These studies, which include investigation of immune mechanisms, seek to define the chemical interactions essential for the transformation of normal to malignant cells. The data obtained are providing a building body of information on additional insights into the manner by which chemical agents change cells during cancer induction.

The discovery and development of rapid and reliable bioassay procedures for the determination and measurement of carcinogenic potential continues to be a major goal of the organization, and progress continues in the development of new, important tools for the meaningful bioassay of chemicals and other materials suspected of carcinogenic activity, though at a pace insufficient to match the rate of introduction of new chemical agents into use by society.

In 1969 these programs will be continued at approximately the same level. There will be a modest increase in the program of bioassay research on substances judged likely to constitute cancer-causing hazards to public health. This will be accomplished through reduction of research aimed at understanding the mechanisms by which cancer-causing chemicals act.

### Solid Tumor-Virus and Special Virus Leukemia

Activities within the Viral Oncology area are staffed with specialists in the scientific disciplines specifically needed to conduct comprehensive basic research on all aspects of virus-cancer relationships, and to manage the related

program of developmental and applied research that is essential to the achievement of the goals of the National Cancer Institute with respect to viral oncology.

The Viral Oncology program is composed principally of two research and development program areas--the Special Virus Leukemia Program (SVLP) and the Solid Tumor-Virus Program (STVP). Two other program areas--Program Resources and Logistics and Biohazards Control and Containment--provide relevant support to the SVLP and STVP.

The Special Virus Leukemia Program is conceptually based on the assumption that viruses are causally associated with leukemia and lymphoma in man. This assumption is based largely upon experience with many laboratory and domestic animals in which causal associations have been established. The purpose in establishing this program has been to accelerate the progress of research directed to clarifying the viral role in human cancer causation, using leukemia as the major model system. Ultimately, if viral agents can be identified and shown to be causative, it may be possible to develop and produce effective vaccines and other modes of treatment to prevent or cure leukemia and other virus-induced cancers. Cancers have been prevented in experimental animals by these means.

It is now apparent that virus-like particles of at least two different types can be detected in--and in some cases isolated from--tissues of leukemia and lymphoma patients around the world. These are a herpes-type virus (HTV) similar to those causing "cold sores" and a C-type which resembles in shape viruses causing animal murine leukemias. The herpes-type virus has been the one virus most persistently detected. Data collected through the program during the past three years now permit conclusion that the HTV is not uniquely associated with Burkitt lymphoma, but may, like poliomyelitis viruses, be ubiquitous, though perhaps causing disease in only relatively few cases. At least 42 of the more than 60 tissue cultures established from cells of patients with leukemia and lymphoma contain the HTV. In addition, this virus has been found, prior to culture, in tissues of leukemia patients, in representatives of animal species, in people with non-cancerous diseases, and in "normal" healthy individuals. The wide-spread distribution of this virus, therefore, suggests that, if it is related to leukemia or lymphoma, a "normal" non-diseased carrier may be a source of infection for highly susceptible individuals. The very recent finding, by scientists within this program, that a herpes-type virus is causatively related to infectious mononucleosis gives strong added credence to the assumption that these viruses may be associated with the causation of leukemia and lymphoma in man. The successful production and purification of several different isolates of the herpes-type virus have made it possible to conduct necessary studies to determine which of nine different serological tests most effectively detects and quantifies the HTV antigens or antibody in human materials. Comparative tests are planned during 1968 which may then make it possible to screen large numbers of human sera and tissue for the presence and amount of antibody or antigens which will indicate which subjects have been infected with HTV. It is still unknown how many different major antigens are associated with the herpes-type viruses isolated from over 60 leukemia and lymphoma patients. A full-scale definitive serological survey, therefore, must await this determination.

The Solid Tumor-Virus Program area of the SVLP has been established and instituted this year to study the action of DNA viruses in the induction of 'solid' tumors, sarcomas and carcinomas, a much larger group of cancers than the leukemias and lymphomas. Important developments from animal studies are giving additional understanding of the induction of solid tumors with this type of virus (DNA) and some direct studies in man can now be instituted. The purpose in establishing this program area has been to accelerate and coordinate the progress of research directed toward the understanding of the role of the DNA viruses in human cancer causation and to complement the studies on the leukemia-causing RNA viruses now underway in the SVLP.

A special report has been prepared for the Hearings to provide a comprehensive description of the total Virus Cancer program and detailed progress to date.

In other programs concerned with Viral Oncology, scientists will continue studies on the detection and replication of the C-type particles from human leukemia and lymphoma. Success has not yet been achieved in obtaining large amounts of C-type virus, although many techniques that work in animal systems have been tried. Collaborative studies conducted by clinical and laboratory investigators during the past year have now made it possible to collect very large fractions of blood suspected of containing the particles. Within 1968, this material will be used in comparative studies of the human C-type virus, the mouse and chicken leukemia viruses, and the herpes-type virus. An important new technique for detecting and measuring C-type mouse leukemia viruses was also developed during the past year. It is now possible, in tissue cultures, to detect the presence of "soluble antigens", inner components of infected cells resulting from inoculation of even minute quantities of virus. Using this method, scientists have isolated and propagated in tissue culture over 100 new strains of viruses related to the mouse leukemia family. Many of those tested have been found non-leukemogenic but capable of acting as "helpers" in the induction of tumors by an otherwise defective mouse sarcoma virus. These studies provide some insight into possiblities as to why we have not yet been successful in growing quantities of virus from human tissues and provide additional approaches for moving ahead with studies directly related to man.

The Viral Oncology area will continue at the same approximate level in 1969. A modest step forward in both the Special Virus Leukemia Program and the Solid Tumor-Virus Program will be accomplished through reduction of current activities providing certain resources, especially tissue procurement efforts. In the SVLP, this will be directed at (a) determining cancer-causing activity (in animals) of viruses already isolated from human cancer, and (b) relating this activity and other characteristics of the candidate viruses to establish firm evidence that these agents cause cancer in man. In the Solid Tumor-Virus Program the only additional activities will be concerned with the initiation of studies of the incidence of leukemia-sarcoma viruses in man and domestic animals, including attempts to clarify the significance of the "helper" viruses.

Cancer Therapy

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Total | 390 | $27,069,000 | 390 | $27,136,000 | --- | +$67,000 |
| Office of the Scientific Director | 78 | 1,467,000 | 78 | 1,480,000 | --- | +13,000 |
| Clinical Trials | 77 | 915,000 | 77 | 927,000 | --- | +12,000 |
| Experimental Therapeutics | 43 | 581,000 | 43 | 589,000 | --- | +8,000 |
| Cancer Chemotherapy National Service Center | 57 | 718,000 | 57 | 727,000 | --- | +9,000 |
| Therapy Contracts | --- | 19,620,000 | --- | 19,627,000 | --- | +7,000 |
| Baltimore Cancer Research Center | 38 | 719,000 | 38 | 727,000 | --- | +8,000 |
| Allocation to VA | 82 | 1,030,000 | 82 | 1,038,000 | --- | +8,000 |
| Special Virus-Leukemia: | | | | | | |
| Direct operations | 15 | 419,000 | 15 | 421,000 | --- | +2,000 |
| Contracts | --- | 1,600,000 | --- | 1,600,000 | --- | --- |

Introduction

The objectives of the Cancer Therapy program are to find drugs that will cure cancer and to make it possible for physicians to use them safely for the control of all malignant diseases. The National Cancer Institute's coordinated program has achieved these purposes for several rapidly growing cancers. The methods and principles successful for those few diseases present opportunities for exploitation in the common cancers of man. The program is a coordinated one in that it assumes responsibility for the search for new drugs, their study in animals and patients, research on how the drugs work, and the supply of materials and services to extend the useful drugs to the whole country. In order to accomplish this, the program involves direct research in laboratories and clinics, and the wide use of both contracts and grants in obtaining the assistance of universities and industry.

Because of the rapid increase in knowledge about the drug control of cancer, it has been possible to sharpen considerably the objectives of the Cancer Therapy program. It is now clear that these are two biologically different problems represented in the chemical control of the fast growing, as opposed to the slow growing tumors. The reasons for these differences in biology and in drug responsiveness are emerging from an intensive study of cell kinetics, that is, the rates at which different tumor cells divide, the fraction of cells that are dividing, and the ways in which drugs act upon dividing and non-dividing (resting) cells. The drug development program has been completely revised in the past year in order to enable rapid pursuit of new compounds as they can be shown to relate to these newly discovered principles. This redirection will be accomplished by extensive program shifts and will be funded through reduction or deletion of existing programs.

Program Plans in 1968 and 1969

The study of the relation of drug responsiveness of tumors to their cell kinetics has become the scientific base of the Cancer Therapy program. In a practical sense, the more rapidly growing a tumor, the more frequently must the drug be given. The difficulty of application of this simple concept to the clinic arises from the following:

1. The rate of cell division may not be reflected by the rate at which the tumor enlarges, so that measurements of cell division must be individualized at least for each tumor type, and perhaps for each patient within a given tumor type;

2. The ideal dose schedule for a tumor dividing at a particular rate may have to be modified because of the toxicity of that schedule for normal cells such as the bone marrow;

3. The ideal drug schedule may also require modification, because of the clinical pharmacology of the drug (the way in which the patient disposes of the drug);

4. Drug control of slow growing tumors requires much longer duration of drug administration than the fast growing tumors.

The replanning of the Cancer Therapy program in 1968 expanded studies on cell kinetics, and revised studies in toxicology and pharmacology in animals in order to find out as much as possible about the influence of different dose schedules upon tumor cells and the normal animal. The latter studies are carried on primarily by the Experimental Therapeutics area through its intramural and contracts program. The acquisition of new drugs for study and their screening for anti-tumor activity have been re-examined with an eye toward their specific abilities to kill fast growing or slow growing tumors. Extensive efforts are underway to match the chemical structures of known active drugs with their influences on cell kinetics of the two types, and to have synthesized modified structures that will be more selectively toxic--that is, kill tumor cells rather than normal cells. Major responsibilities for efforts in these areas have been assigned to the Cancer Chemotherapy National Service Center.

The primary screen for selecting the most promising drugs has been re-examined for its relation to the new scientific base. It is clear that it selects drugs effective in fast growing tumors. Search is underway to identify animal tumors that will select drugs for slow growing tumors, or at least indicate the best way to use the known drugs to obtain effects on the slow growing tumors. Since drug schedule emerges as the key to gaining better drug control of nonresponding tumors, marked shifts have been made in the directions of toxicology and pharmacology studies. Finally, the implications of these studies for clinical trials have been under re-examination. Since the best use of drugs involves a high degree of individualization in matching dose schedule to tumor growth rate, clinical trials are changing in 2 ways:

1. Techniques are under development to measure the growth rates of tumors so that the ideal dose schedule can be chosen;

2. The high degree of individualization of treatment now possible will require the help of a few highly specialized centers for this type of patient care with less dependence upon large cooperative groups.

There has been continued research and development of better supportive care for patients. This enables larger doses of drugs to be given with greater safety. Platelet replacement has become an accepted part of chemotherapy clinical investigation and the use of frozen platelets is increasing. Better protection against infection is being achieved through improvement in "Life Island" isolation and through perfection of the cell separator to harvest white cells to fight infection.

The therapy portion of the SVLP program provides funding for the partial support of such Cancer Therapy activities as improved supportive care, pharmacology and toxicology studies and the purchase of blood and clinical anti-leukemic drugs.

It is planned that partial renovations and partial equipping will be completed for the pharmacology laboratories at the Baltimore Public Health Service Hospital in 1968. The laboratories will commence operations on a limited scale and in conjunction with the on-going clinical activities will form an integrated program of research on the therapy and management of cancer patients.

Finally, there has been considerable activity among the various task forces, which more and more have become the focus through which new proven research facts can be made available to the specialists treating these cancers.

In the preclinical drug development areas for 1969, the primary screen will be modified since both animal systems now used are selecting drugs for fast growing tumors. One of these two systems (The Walker 256 rat tumor) will be dropped, and replaced by a projected system predictive for slow growing tumors. There will be extensive expansion of dose schedule studies in animals both for therapeutic effect and for toxicity. Pharmacologic disposition studies will be expanded, since this relates blood levels in the various species, including man, to the effects noted with different dose schedules.

Within existing resources changes are being made in the clinical trials portions of drug development. It is planned to strengthen a few already existing centers that will become the major means of carrying out the highly individualized studies now required in tumor growth rates, dose schedules, pharmacology and supportive care. This will be accomplished as follows:

1. Strengthening of the direct clinical operation at the Clinical Center, Bethesda and the U. S. Public Health Service Hospital in Baltimore. In addition, greater use will be made of the joint effort with the Veterans Administration, especially at the V. A. Hospital in Washington, D. C.

2. Contracts will be negotiated with 3 centers already working closely with NCI on the probems of intensive clinical trials; namely, M. D. Anderson Tumor Clinic, Childrens Hospital in Philadelphia and Childrens Hospital, Los Angeles.

3. The key question in clinical chemotherapy is to relate rates of cell growth to drug susceptibility. This requires the intensive study of relatively few patients who must receive extensive supportive care. It is planned to extend the capabilities of the 3 directly operated units (see 1 above) and those of the 3 contractors (see 2 above), so that they will not only be centers capable of giving the most modern management of widespread cancer, but possess the resources required for intensive investigation related to cell kinetics. This will include provision of cell separators for white cells and frozen platelets. It also envisions the transfer of protected environment studies from the "Life Island" concept to the use of laminar flow.

4. The major efforts in the clinic will be to use the new knowledge on drug schedules and cell kinetics, to see if the fast growing tumors can now be cured, and the slow growing tumors controlled to the degree now possible for the fast growing tumors.

Cancer Task Forces

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Total..... | 12 | $2,805,000 | 37 | $4,707,000 | +25 | +$1,902,000 |
| Breast Cancer & Other Task Forces..... | 12 | 2,805,000 | 15 | 3,307,000 | +3 | +502,000 |
| Lung Cancer Task Force..... | --- | --- | 22 | 1,400,000 | +22 | +1,400,000 |

Introduction

The line item, "Cancer Task Forces", appears for the first time in this submission. The purpose of this item is to bring together into one area of the budget additional costs of operating various Cancer Task Forces under NCI allocations. Some of the recently constituted Task Forces have been called on to consider multiple aspects of specific disease problems, e.g. etiology, diagnosis and therapy. Programs generated from their activities thus will tend to cut across organization lines and depend on a variety of ongoing activities within the Institute.

The first of these task forces, the Breast Cancer Task Force, was established in April of 1966 with funds earmarked by Congress in the NCI appropriation. This task force considers the problems of causation of Breast Cancer as well as those of improved methods of diagnosis and therapy. The task force represents a variety of disciplines involved in research on this disease, including endocrinology, chemotherapy, surgery, radiology, virology, and epidemiology. The task force serves as the operating and coordinating mechanism for an intensified program of clinical and nonclinical research

The Cancer Institute has established several other task forces or study groups. Generally, there are no specific funds allocated for their use. They exist and work through the established organizational set-up, evaluating the present state of knowledge and planning future research efforts without regards to cost figures. They identify major problem areas, formulate general research objectives, and as the state of the art permits, plan and recommend specific programs and projects for implementation.

The Lung Cancer Task Force has recently been established in accordance with the direction of the President. Preliminary planning efforts have centered on the possibilities of establishing programs in the areas of: Etiology and Prevention and Clinical Management as well as an Educational Program. These major areas can, in turn, be considered in terms of a number of lines of research attack which include development of a less hazardous cigarette, identification and modification of industrial-atmospheric-occupational hazards and improved methods of detection, diagnosis and treatment

of lung cancer. Also, the research program will be supplemented by a program which in collaboration with the National Clearinghouse on Smoking and Health will produce and disseminate educational materials with the objective of providing the various population groups with the most current information on the problem of lung cancer.

Program Plans in 1968 and 1969

Breast Cancer and Other Task Forces

The Breast Cancer Task Force during 1968 continued to make progress in the concerted effort to understand the causes of breast cancer and to determine methods of improved treatment. Analysis of cooperative clinical studies indicates that chemotherapy given as an adjuvant to surgical therapy has measurably improved the condition of breast cancer patients. Also, certain viruses have been identified as causing mammary tumors in laboratory animals. Increased efforts have been undertaken to relate these findings to determine the role of viruses in causation of human breast cancer.

Other NCI task forces and study groups relating to Acute Leukemia, Clinical Trials, Solid Tumors, Choriocarcinoma, Chronic Leukemias and Multiple Myeloma, Lymphoma, Colon-Rectum, Prostate-Bladder, and Brain Tumors continued in 1968 to study specific areas of the cancer problem.

In 1969, a net increase of $502,000 and 3 positions is requested to extend the clinical studies of breast cancer now conducted by the several cooperative groups in the efforts to improve early detection and chemotherapy of breast cancer. The active exploration of the role of hormonal factors in the development of breast cancer and studies relating to the prevention of the disease will continue.

Lung Cancer Task Force

During 1968, the NCI staff assisted the recently formed Lung Cancer Task Force in laying out a variety of general research approaches to the disease. Plans thus far indicate that research efforts will be in two major areas: Etiology and Prevention and Clinical Management of the Disease. It is anticipated that completion of detailed plans in 1968 will permit formulation and implementation of specific programs in 1969.

An increase of $1,400,000 and 22 positions is requested to support the Lung Cancer Task Force for 1969. This is the first year that funds have been budgeted for this item. During 1969, specific plans for selected research programs will be ready for implementation. One high priority program is the establishment of the assay systems which will form the basis for the eventual development of a less hazardous cigarette. Of the total amount requested for the support of this and other programs, $1,100,000 will be used for contract research.

## Supporting Services

Supporting Services is primarily a service oriented unit of the National Cancer Institute which provides the whole Institute with selected administrative and office services. Also included in this item is the editorial review and publication of the Journal of the National Cancer Institute.

In 1969, the amount of funds requested will enable the National Cancer Institute to continue this type of support to the Institute as well as the continued support of the NCI Journal. Also, in 1969, a portion of the total funds will be used to cover costs of moving into the new cancer building.

The Collaborative Research and Development area includes a request of $116,000 for annualization of the 1968 pay raise in 1969. There is also an increase of $18,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Biometry, Epidemiology, and Field Studies

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 112 | $1,063,000 | 112 | $1,081,000 | --- | +$18,000 |
| Other expenses..... | --- | 352,000 | --- | 354,000 | --- | +2,000 |
| Total..... | 112 | 1,415,000 | 112 | 1,435,000 | --- | +20,000 |

Introduction

Characterization of the occurrence and behavior of cancers by specific sites in human populations, both in the United States and abroad; the effects of migration on these cancer patterns; and the search for environmental and other factors associated with differenct types of cancers continue to be of major concern to the organizational groups funded under this budget activity.

A description of how the National Cancer Institute's Demography programs relate to other activities with which they are associated organizationally may be found in the introduction to the Etiology area under "Collaborative Research and Development."

Program Plans in 1968 and 1969

During this year, the Epidemiology Branch plans to continue studies on the concurrence between congenital defects and cancers. A visual review of 22,000 death certificates in the National Registry of Childhood Cancer Deaths has revealed possible associations between specific congenital defects and childhood neoplasms among siblings. Substantiation of these associations would provide useful insights into the factors responsible for childhood malignancy. Animal disease data will continue to be observed. For example, recent examination of veterinary cancer data indicates that the larger breeds of dogs have 200 times the risk of bone sarcoma compared with small breeds and that boxers exhibit an increased risk of lymphoma. Animal studies may well have significance in the selection of animals for laboratory research but, more important, will provide the opportunity to observe comparative disease models which may speed the identification of factors responsible for cancer in man.

The Biometry Branch (Statistics and Applied Mathematics Group), through the interaction of mass data and evolving mathematical models, provides the competence for planning, evaluating, and reporting the results of experimental cancer therapy in man, and for evaluating the worth of diagnostic techniques. The Third National Cancer Survey, following a pretest in Birmingham, Alabama, in the spring of 1968, will be conducted in 1969-1971 in 10 metropolitan areas and two states to provide up-to-date information on cancer incidence, prevalence, and some indexes of the economic and societal impact of cancer. The

current program of end-results evaluation, mathematical development, and demographic studies will be continued with emphasis in the latter program on studies of cancer patterns in migrant populations to help separate external environment causes of cancer from internal environmental (genetic) causes--and so provide possible bases for cancer prevention.

The Epidemiologic Pathology Unit plans to continue its close collaboration with other components of the Etiology area. The bringing together of data and concepts from pathology, biometry, and epidemiology in an integrated fashion permits detections of additional associations of factors with cancers and affords added insights into causation and prevention. Specific effort will be directed to human and animal lymphomas and leukemias.

The above functions will continue at the same level in 1969. To be able to continue the Third National Cancer Survey, planned consultative epidemiologic and biometric assistance to the Regional Medical Program and certain other activities will be limited. Activities of the Cancer Survey project during 1969 will include processing and analyzing results of the pretest; redesigning and developing forms; eliciting cooperation in all field areas; establishing contracts; writing instruction manuals for supervisors, interviewers and coders; conducting training programs; and developing a data processing system, including the writing and testing of certain computer programs for editing and tabulating data.

An increase of $13,000 is requested for annualization of the 1968 pay raise and $5,000 for an extra day of pay in 1969. There is also an increase of $2,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Review and Approval of Grants

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 111 | $1,103,000 | 113 | $1,141,000 | +2 | +$38,000 |
| Other expenses..... | --- | 1,439,000 | --- | 1,379,000 | --- | -60,000 |
| Total..... | 111 | 2,542,000 | 113 | 2,520,000 | +2 | -22,000 |

This activity under the Associate Director for Extramural Activities supports the administrative staff for all contract activities of the National Cancer Institute and both the scientific and administrative staff responsible for the review of all cancer grants. The staff obtains the necessary information regarding all grant applications and in cooperation with study groups makes recommendations for the consideration of the National Advisory Cancer Council which recommends approval or disapproval of grant applications.

The program increase of $25,000 and 2 positions will provide one scientist and one secretary in support of the expanding field of immunology which is concerned with the bacteriological science and chemical treatment in resisting development of a given disease.

An increase of $14,000 is requested for annualization of the 1968 pay raise and $4,000 for the extra day of pay in 1969. There is a decrease of $65,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Program Direction

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 56 | $716,000 | 58 | $746,000 | +2 | +$30,000 |
| Other expenses..... | --- | 600,000 | --- | 547,000 | --- | -53,000 |
| Total..... | 56 | 1,316,000 | 58 | 1,293,000 | +2 | -23,000 |

This activity provides for the overall administration and direction of the programs of the Institute. The Director and his staff give professional leadership and technical guidance to the varied activities of the Institute.

The program increase of $45,000 and 2 positions will increase the operations research and systems communication aspects of the program planning activity for application in such selected areas as increased automation and computer technological utilization in laboratory operation.

An increase of $8,000 is requested for annualization of the 1968 pay raise and $2,000 for the extra day of pay in 1969. This is offset by a decrease of $78,000 for centrally furnished services from the "National Institutes of Health Management Fund."

# NATIONAL HEART INSTITUTE

## WITNESSES

DR. DONALD S. FREDRICKSON, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. THEODORE COOPER, ASSOCIATE DIRECTOR, ARTIFICIAL HEART-MYOCARDIAL INFARCTION PROGRAM, NATIONAL HEART INSTITUTE
R. H. HENSCHEL, EXECUTIVE OFFICER, NATIONAL HEART INSTITUTE
JOHN H. REEDER, BUDGET OFFICER, NATIONAL HEART INSTITUTE
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimated | 1969 estimated |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 5,734 | 5,875 | 6,087 |
| Positions other than permanent | 202 | 235 | 245 |
| Other personnel compensation | 56 | 63 | 63 |
| Total personnel compensation | 5,992 | 6,173 | 6,395 |
| Personnel benefits | 659 | 739 | 753 |
| Travel and transportation of persons | 260 | 288 | 300 |
| Transportation of things | 86 | 84 | 90 |
| Rent, communications, and utilities | 213 | 221 | 222 |
| Printing and reproduction | 21 | 20 | 22 |
| Other services | 782 | 1,340 | 1,583 |
| Project contracts | 16,746 | 17,180 | 19,180 |
| Payments to "National Institutes of Health management fund" | 6,555 | 7,071 | 7,169 |
| Supplies and materials | 1,124 | 1,677 | 1,767 |
| Equipment | 711 | 736 | 787 |
| Grants, subsidies, and contributions | 130,415 | 130,235 | 131,483 |
| Insurance claims and indemnities | 4 | | |
| Subtotal | 163,568 | 165,764 | 169,751 |
| Quarters and subsistence charges | −16 | −16 | −16 |
| Total obligations | 163,552 | 165,748 | 169,735 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 695 | 682 | 701 |
| Full-time equivalent of other positions | 38 | 38 | 39 |
| Average number of all employees | 627 | 669 | 699 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1967 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 106,155 | 105,100 | 105,729 |
| (b) Fellowships | 6,508 | 7,439 | 7,604 |
| (c) Training | 17,752 | 17,696 | 18,150 |
| Total grants | 130,415 | 130,235 | 131,483 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 11,406 | 13,113 | 13,671 |
| (b) Collaborative research and development | 3,739 | 17,138 | 19,142 |
| (c) Biometry, epidemiology, and field studies | 1,784 | 1,747 | 1,765 |
| (d) Training activities | 235 | 222 | 224 |
| (e) Review and approval of grants | 2,484 | 2,495 | 2,611 |
| (f) Program direction | 655 | 798 | 839 |
| Total direct operations | 20,303 | 35,513 | 38,252 |
| Total program costs, funded [1] | 150,718 | 165,748 | 169,735 |
| Change in selected resources [2] | 12,834 | | |
| Total obligations | 163,552 | 165,748 | 169,735 |
| Financing: | | | |
| Comparative transfers to other accounts | 781 | | |
| Unobligated balance lapsing | 425 | 150 | |
| New obligational authority | 164,758 | 165,898 | 169,735 |
| New obligational authority: | | | |
| Appropriation | 164,770 | 167,954 | 169,735 |
| Transferred to other accounts | −12 | −163 | |
| Appropriation (adjusted) | 164,758 | 167,791 | 169,735 |
| Proposed transfer to other accounts for pay increases | | −1,893 | |
| Relation of obligations to expenditures: | | | |
| Total obligations | 163,552 | 165,748 | 169,735 |
| Receipts and other offsets (items 11–17) | 781 | | |
| Obligations affecting expenditures | 164,333 | 165,748 | 169,735 |
| Obligated balance, start of year | 92,773 | 113,459 | 128,742 |
| Obligated balance, end of year | −113,459 | −128,742 | −146,477 |
| Adjustments in expired accounts | −3,806 | | |
| Expenditures | 139,841 | 150,465 | 152,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 60,851 | 64,322 | 67,000 |
| Out of prior authorizations | 78,990 | 86,143 | 85,000 |

[1] Includes capital outlay as follows; 1967, $620 thousand; 1968, $736 thousand; 1969, $787 thousand.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $4,441 thousand; 1967, $17,275 thousand; 1968, $17,275 thousand; 1969, $17,275 thousand.

Mr. FLOOD. We now have the National Heart Institution, Dr. Donald S. Fredrickson, the Director, will make the presentation.

We have a biographical sketch of the doctor which we will place in the record at this point.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

(Biographical sketch follows:)

PUBLIC HEALTH SERVICE—NATIONAL HEART INSTITUTE

Name: Donald S. Fredrickson, M.D.
Position: Director, National Heart Institute.
Birthplace and date: Canon City, Colo.; August 8, 1924.
Education:
June 1942: graduated from high school.
June 1946: B.S., University of Michigan.
June 1949: M.D., University of Michigan.
Experience:
1966 to present: Director, National Heart Institute; Chief, Laboratory of Molecular Diseases, NHI.

1962–1966; Head, Section on Molecular Diseases, Laboratory of Metabolism, NHI.
1961–66: Clinical Director, NHI.
1955–61: Member, Senior Research Staff, Laboratory of Cellular Physiology and Metabolism, NHI.
1953–55: Clinical associate, NHI.
1952–53: Research fellow in medicine, Massachusetts General Hospital, Boston.
1950–52: Assistant in medicine, Peter Bent Brigham Hospital, Boston.
1950–51: James Jackson Cabot research fellow in Medicine, Harvard Medical School, Boston.
1949–50: House officer, Peter Bent Brigham Hospital, Boston.

Association memberships: American Heart Association, Association of American Physicians, American Oil Chemists' Society, American Physiological Society, American Society of Human Genetics, American Society for Clinical Investigation, American Association for the Advancement of Science, American College of Cardiology, American College of Physicians, American Medical Association, Phi Beta Kappa, Phi Kappa Phi, Washington Society of Pathologists.

Special awards, citations, or publications:
Honorary member of the Medical Society of Sweden.
Coeditor, "The Metabolic Basis of Inherited Disease."
Member of the Publications Committee of the American Physiological Society.
Member of editorial boards of the Journal of Clinical Investigation, Journal of Lipid Research, and Physiology for Physicians.
Author or coauthor of approximately 100 scientific papers.

Mr. FLOOD. I see you have a statement, Doctor. How do you wish to proceed.

Dr. FREDRICKSON. With your permission, I would like to read it if I may.

Mr. FLOOD. All right.

Dr. Fredrickson.

GENERAL STATEMENT

Mr. Chairman and members of the committee, in this short statement, I would like to touch briefly on progress made during the past year in several Heart Institute programs that I believe will be of special interest to the committee.

ARTIFICIAL HEART-MYOCARDIAL INFARCTION

This year the Artificial Heart-Myocardial Infarction program took its first steps toward the goal of focusing more of the Nation's outstanding research talent upon the acute heart attack, which annually causes over 140,000 deaths in Americans under 65 alone. The first five myocardial infarction research units were established. This year we plan to add three or four more units toward the planned network of 12. They will combine unexcelled medical care with intensive clinical and laboratory research involving many disciplines. The aim is better salvage techniques widely applicable to acute coronary care. We are encouraged by the promise of this program and by the extraordinary interest in it shown by the medical community.

Mr. FLOOD. What is myocardial infarction?

Dr. FREDRICKSON. That is the large word for heart attack, sir; coronary attacks.

Mr. FLOOD. Go ahead.

Dr. FREDRICKSON. The Institute also awarded 41 new contracts and extended 16 others in support of research on artificial hearts and on the development of techniques and devices for temporary cardiac assistance. The feasibility of salvaging a patient by mechanical assistance has been demonstrated. We feel it is urgent to accelerate the necessary bioengineering and physiological studies related to development of the broad area of assisted-circulation techniques.

Recent dramatic achievements have merged the development of mechanical hearts with transplantation into a general problem of cardiac replacement. We believe that development of these two possibilities should proceed collaterally. Major obstacles to transplantation are tissue rejection and preservation of donor tissues. The Institute presently supports 64 projects, totaling about $1.3 million, in the heart-transplantation field. This program will be strengthened as available funds permit.

ARTERIOSCLEROSIS AND HYPERTENSION

At the same time, research to develop means of preventing premature arteriosclerosis and controlling hypertension must remain paramount goals. Research is yielding much greater insight into these two major killers and providing opportunities for clinical application of promising discoveries. One such coordinated field trail, the coronary drug projects, is testing the ability of four lipid-lowering drugs to reduce mortality rates among men who have recovered from a heart attack. The enrollment of the necessary 55 clinics is completed, as of March 1, Mr. Chairman, and 2,962 of the needed 8,500 patients have already been recruited.

In their report on the national diet-heart feasibility study, the investigators concluded that the blood cholesterol levels of Americans could be reduced by diet.

CHLORESTEROL

Mr. FLOOD. Has there not developed within recent years an anti-school of thought on the vital importance of cholesterol in these problems? Is there not a school of thought which says this has been highly overplayed?

Dr. FREDERICKSON. I should think it is probably more correct to say there still remains a very large body of scientific opinion which wants more proof.

Mr. FLOOD. Scientific opinion?

Dr. FREDRICKSON. Scientific and medical opinion both which requests more proof that lowering cholesterol will reduce the amount of heart attacks before we can make sweeping recommendations to the American public.

Mr. FLOOD. Then it is not a new school; it is a division of opinion?

Dr. FREDRICKSON. It is a very real division of opinion.

Mr. FLOOD. I am sure the medical community is aware of this, but the public, I believe, have been sold completely on the importance of cholesterol in causing heart trouble. Do you think that is so?

Dr. FREDRICKSON. I think you are correct, Mr. Chairman.

First of all, the discussion in the public press about cholesterol itself focuses attention on that, and the attention perhaps has tended to be a negative one.

Frankly, I think the state of the art is as follows: That we now know enough to begin a definitive trial to really find out if the positive or negative side is correct. And I think that this is the direction in which we must move.

Mr. FLOOD. What is cholesterol?

Dr. FREDRICKSON. Cholesterol is a rather complex molecule found in all tissues of the body and in the bloodstream. It is made by the body in most tissues except the adult brain, and we get it in our food from animal sources. Plants do not have cholesterol per se. They have similar molecules.

Mr. FLOOD. Why is it such a bad actor, if it is?

Dr. FREDRICKSON. Evidence implicating cholesterol in arteriosclerosis or hardening of the arteries goes back to the turn of the 20th century when it was discovered by feeding cholesterol to animals that it was possible to produce severe arteriosclerosis, and since that time a great deal of evidence has accumulated, not only that one can do this in animals, but it is very clear that an individual with higher cholesterol is more likely to have an acute heart attack or coronary disease than one with low cholesterol.

Mr. FLOOD. Is diet the only cure?

Dr. FREDRICKSON. No, I am sure it is only one of many possible things.

Mr. FLOOD. Proceed, Doctor.

Dr. FREDRICKSON. They recommended a study of sufficent size and duration to test whether such diets will cut the incidence of coronary artery disease. We are now carefully determining, with additional expert opinion, our recommendations on this important challenge.

I should perhaps interpolate there that of all the cardiovascular diseases, it is only in arteriosclerosis, which is the major single killer in the population, that have we failed to note a downward trend in the past 10 years in the death rate.

### NATIONAL BLOOD RESOURCE PROGRAM

The goal of the national blood resources program, begun last year, is to improve technology related to the supply and use of whole blood, plasma, or medically important blood fractions. Now being supported is research to develop means for the large-scale production of cellular and protein components of blood and to evaluate chemical preservatives for reducing losses of whole blood through outdating.

### CLOT-DISSOLVING AGENTS

A cooperative clinical trial of the clot-dissolving agents urokinase and streptokinase is expected to begin this year. Initially, the drugs will be tested against clots obstructing bloodflow in the lungs. However, if initial results are promising, they will probably be tested against coronary occlusion in future studies.

Mr. FLOOD. Do all internal clots get in the bloodstream?

Dr. FREDRICKSON. Some clots that remain where they are formed are called thrombi, and these are very important medical problems as well. When these clots move to another site, they are called emboli. So clots both stay where they form and also move around. It is the ones that tend to move around that are in the main perhaps the most serious.

Substantial progress was also made during the year in the Institute's own research and through its regular grant-support programs. Our research highlights document presents a few of the noteworthy advances achieved through these programs in the prevention, diagnosis, and treatment of cardiovascular diseases.

SUMMARY OF BUDGET REQUEST

In conclusion, Mr. Chairman, the request for the National Heart Institute is $169,735,000 for 1969 as compared with an operating level of $165,748,000 in 1968, an increase of $3,987,000. Of the requested increase, $1,248,000 will be allocated for extramural research and training activities as follows: $629,000 for research grants, $165,000 for fellowships, and $454,000 for training grants. The remaining $2,739,000 will be allocated for direct operations to provide an increase of $558,000 for laboratory and clinical research, $2,004,000 for collaborative research and development in the artificial heart-myocardial infarction program, and $177,000 for biometry, epidemiology, and field studies, for the review and approval of grants, and for program direction.

I shall now be happy to answer any questions the committee might have.

Mr. FLOOD. Those figures you gave us for the 1969 budget amount to about a 2½-percent increase over your operating level for 1968.

Dr. FREDRICKSON. Yes, sir.

EFFECT OF BUDGET ON PROGRAM

Mr. FLOOD. You show small dollar increases for your grant programs, but not enough to cover the increased costs of maintaining the programs at the current level.

You have a reduction of 232 in the number of research grants, a reduction of 15 in fellowships, a reduction of 17 in training grants. How is this going to affect your program?

Dr. FREDRICKSON. I anticipate, sir, we shall actually have closer to 300 grants approved that we will be unable to fund.

Mr. FLOOD. What is that going to do to your program?

Dr. FREDRICKSON. I think it is going to mean considerable tightening of the belt. It will mean that some areas that might develop more rapidly will certainly be retarded in their development, and that we will have the opportunity to train fewer individuals in the field of cardiovascular science and medicine than we might have at another time.

Mr. FLOOD. Is it material? Is it serious? Is it of great importance? Or is it just one of those things?

Dr. FREDRICKSON. I feel very strongly that the programs of the Heart Institute actually represent both in research and training the best determinants or major determinants of the quantity and quality of cardiovascular care in this country.

There are 16 million Americans with heart disease at this time, sir, and each of the physicians who must treat these people, if they are stroke or angina or heart attack. . . .

Mr. FLOOD. With regard to grants for research on atherosclerosis, your justifications say:

> During the past decade there has been nearly a tenfold increase in the number of research projects in this field.

What do we gain from all of this action? Tenfold, that is a lot.

Dr. SHANNON. It is a large or small amount, depending on the starting base.

Ten years ago there was so little work going on in the field as not to be significant. So I would say in a field as important as this, a tenfold increase does not represent an increase that truly reflects the importance of the field.

Actually, over this 10-year period we have been able to bring diverse talent into this field—biochemists, physical chemists, physiologists, pharmacologists, and the like.

I am disappointed that we have not been able to attract more talent into this field, particularly into those areas that are examining the underlying biological mechanism.

Mr. FLOOD. We have had lots of action and lots of people in this. What do we gain from it?

Dr. SHANNON. I think Dr. Fredrickson can answer that.

Dr. FREDRICKSON. In the first instance, the funding for arteriosclerosis is divided into two major problems: That of understanding the cause of disease and hence leading to the prevention, and the other leading to a means to increase the rate of salvage of patients who already have the disease.

I think we have achieved a major step toward the move toward prevention. I think that the fact today we are able to mount a drug trial involving nearly 8,000 people, that we are able logically to consider the requirement of the diet study means we have acquired over this time the basic information for making accurate probability calculations of how many people we shall have to use, how much we shall have to lower their blood fat, what kind of a change we might expect.

We can actually now program these large intervention trials. At the same time we have clarified tremendously the influence on the one hand of genes as opposed to the environment, although there are still many mysteries to be solved.

Mr. FLOOD. I think this might be a good place to put the special report with regard to atherosclerosis with particular emphasis on drug and hormone therapy.

(The report follows:)

SPECIAL REPORT:
NATIONAL HEART INSTITUTE
ATHEROSCLEROSIS AND CORONARY HEART DISEASE:
DRUG AND HORMONE THERAPY

While the outlook for survival and rehabilitation of the patient under treatment for a heart attack continues to brighten with advances in cardiac resuscitation and intensive medical care, the risk of developing a heart attack for an asymptomatic American male in his thirties, forties, or fifties remains about one in five. Moreover, mortality from first attacks still runs as high as forty percent, with half of these deaths occurring within one hour of onset. Clearly, then, the effort to reduce the toll of coronary heart disease in this country must concentrate heavily on its population of apparently healthy men and on the identification and control of silent precursors in an attempt to prevent first heart attacks.

## Approaches to Prevention

The central target of this preventive effort is atherosclerosis, because this "mushy hardening" of the arteries is what encroaches on the blood supply to the heart muscle in most cases. The precursors of atherosclerosis are generally the precursors of coronary heart disease.

Atherosclerosis, in turn, may have not one but many causes. "Maleness," advancing age in both sexes, high blood pressure, elevated blood levels of lipid and carbohydrate, psychic stress, dietary fat intake, obesity, sedentary physical habits, and family history of arterial disease: any or all of these factors appear to influence susceptibility to atherosclerosis or to affect the progress of the disease.

Obviously, some of these precursors either cannot or should not be eliminated. However, certain risk factors can be eliminated or ameliorated with the help of a physician, hopefully with beneficial effects in the high-risk population. Fortunately, both of the most serious risk factors--hyperlipidemia and elevated blood pressure--can often be treated successfully.

Hyperlipidemia. The measures in current use to prevent and treat atherosclerosis by reducing blood lipid levels of cholesterol and other fatty substances (collectively called lipids) are hypocholesterolemic agents, hormones, and unsaturated fatty acids. The unsaturated fatty acids are drugs in a technical sense only, for they are a metabolically indispensible part of the ordinary diet and are commonly administered to hyperlipidemic patients in the course of dietary therapy.

Cholesterol is the blood lipid most commonly found to be elevated in association with atherosclerosis and its complications. Mild hypercholesterolemia is usually traceable to habitual dietary patterns; but extremely high blood cholesterol levels also stem from metabolic disorders such as diabetes, hypothyroidism and hereditary hypercholesterolemia, and dietary manipulation alone has limited value in such cases. Even without

these complicating metabolic diseases, only modest reductions in blood cholesterol can usually be expected from dietary modifications that would not seriously inconvenience customary eating habits.

Most therapeutic diets and drugs for the management of elevated blood lipid levels have been aimed at the reduction of blood cholesterol. However, elevated blood cholesterol is only one facet of the larger clinical problem of hyperlipidemia. In turn, NHI studies have shown, hyperlipidemia is not a single entity but at least five, several of which include hypercholesterolemia as one of their manifestations.

The NHI studies have resulted in a rational system for identifying and classifying hyperlipidemias on the basis of serum lipoprotein patterns, easily obtained by low-cost electrophoretic techniques. Under this system, most patients with elevated blood lipids fall conveniently into one of the categories of hyperlipoproteinemia designated as types I-V. This is an important step toward a more systematic approach to clinical management, for standard "cholesterol lowering" regimens are not uniformly effective against all types of hyperlipoproteinemia and may actually aggravate rather than ameliorate one or another of these disorders. In fact, lumping patients with different types of hyperlipoproteinemia under the general heading of "hypercholesterolemia" may be responsible in large measure for the wide individual variability in response to diet or drug regimens frequently observed in clinical trials.

Currently, NHI scientists are attempting to determine which mode of therapy is best suited to each of the five types of hyperlipoproteinemia. The two most common are type II and type III.

Type II is characterized by a relative excess of low-density lipoproteins. It may be an inherited condition, it may be of dietary origin, or it may be a secondary manifestation of certain other metabolic disorders, especially hypothyroidism. It is probably responsible for most cases of "hypercholesterolemia" that the physician is called upon to treat. Type III, though less common than type II, is by no means rare. It too, is characterized by an excess of low-density lipoproteins, especially the very-low-density ones that transport chiefly cholesterol and triglycerides in the blood. Both of these blood lipids are commonly elevated in type III patients. Both types of hyperlipoproteinemia are associated with accelerated development of atherosclerosis. In addition, a common characteristic of both types, if severe, is the appearance of fatty deposits called xanthomas in various soft tissues of the body, particularly around tendons of the hands and feet.

Nineteen patients with each type have been treated with a therapeutic diet containing 40 percent of total calories as fat, chiefly polyunsaturated; 40 percent carbohydrate, and 20 percent protein. Cholesterol intake was limited to 300 mg. per day.

In type II patients, the average blood cholesterol fell from 438 to 330 and triglycerides fell slightly. In type III patients, the cholesterol fell from 486 to 228 and the triglycerides fell from 650 to 194. Thus, the therapeutic diet substantially improved the blood-lipid pattern in type II and nearly normalized it in type III.

Further blood lipid reductions were achieved when the therapeutic diet was supplemented with the lipid-lowering drug CPIB (Clofibrate). In type III patients, the drug reduced cholesterol by an additional 14 percent and triglycerides by 22 percent. The response was still more dramatic in type III patients: cholesterol fell by an additional 29 percent and triglycerides by 44 percent. Therapy resulted in rapid regression of xanthomas in type III patients.

The limitations inherent in dietary therapy alone have spurred the search for drugs which lower blood cholesterol safely and conveniently by some direct action on processes of cholesterol absorption, synthesis, transport or excretion by the body; and some of these are proving effective in reducing the other lipid fractions as well.

Dextrothyroxine is one of the most promising of the synthetic analogs of the thyroid glandular secretions, which stimulate the systemic metabolic rate including cholesterol metabolism. Treatment with these natural hormones has been found effective in reducing blood cholesterol levels; but effective doses often produce hyperthyroid symptoms, including chest pain in coronary patients, as well as tremors and general nervousness. Dextrothyroxine presumably also stimulates cholesterol metabolism, but is more selective in that it is well tolerated by most patients in doses which reduce blood cholesterol levels some 15-25 percent. Many physicians regard dextrothyroxine as the best of the currently available drugs for lowering blood cholesterol levels; but its long-term effectiveness requires further study. Meanwhile the search continues for even more potent and selectively acting thyroid analogs.

Conjugated estrogenic substances, like the aforementioned dextrothyroxine, are products of an effort to improve on the anti-hyperlipidemic activity of natural hormonal substances. It is well known that premenopausal women are much less likely to incur coronary occlusions than men; and that their estrogenic hormones confer such protection along with the female secondary sex characteristics. Long term studies have shown that estrogen administration can exert similar effects in heart-attack cases, sharply reducing the incidence of recurrent attacks and increasing survival rates, but also causing breast development and loss of libido in many. Conjugated estrogenic substances, on the other hand, may confer protection against coronary disease at doses which do not feminize. In studies using conjugated equine estrogens, mortality from recurrent attacks among coronary patients thus treated was more than fifty percent lower than among control patients during the first year and one-half. Thereafter, effects on mortality were somewhat less, but after three years mortality was still a third less than in controls. Although additional

evaluation is needed to settle the controversy concerning the place of estrogenic substances in the prevention of first attacks, the studies thus far suggest that middle-aged men, as well as older or postmenopausal women, who have overt coronary disease or otherwise appear especially prone to such disease may derive substantial protection from treatment with estrogenic substances. They also suggest that this protection need not entail intolerable side effects for either sex.

Chlorophenoxyisobutyrate ester (Clofibrate) is a much newer anti-hyperlipidemic than either of the aforementioned hormonal types, but has already been employed in a large number of laboratory and clinical studies worldwide. Not only does Clofibrate markedly reduce blood cholesterol but it also produces even greater decreases in blood triglycerides, another lipid fraction strongly implicated in the development of atherosclerosis. The drug also seems to inhibit the clumping together of blood platelets, and may thereby confer an additional measure of protection against the thromboembolic complications of heart attacks. The drug has thus far been remarkably free of toxic or unpleasant effects, but it is too new to predict how long this specificity of therapeutic effectiveness will be sustained. Its mechanism of action requires more laboratory investigation, and its effectiveness in preventing first attacks and reducing mortality requires further long-term study in large populations.

Nicotinic acid (niacin) is a B complex vitamin which was found to inhibit the synthesis of cholesterol by the liver when administered in much larger than vitamin doses, such as two to five grams per day for an adult human. It is not yet certain whether this interesting hepatic mechanism of action is altogether responsible for its effectiveness against hypercholesterolemia; but serum cholesterol levels gradually fall to normal or near normal in most patients who faithfully adhere to the high dosage schedules necessary. The toxic effects of the lipid-active dosage--brief flushes, transient gastrointestinal discomforts, and occasional increases in skin pigmentation--are almost always clinically negligible; but they do limit the usefulness of this otherwise excellent drug. This problem could yield to the continuing search for better niacin analogs or chemical structures which act through the same physiologic mechanism, only more specifically. Any chemical structure capable of diminishing circulating cholesterol by diminishing its synthesis by the liver without creating any new hepatic, circulatory or metabolic aberrations more serious and lasting than those of niacin therapy would be promising.

Cholestyramine diverts cholesterol from the vascular compartment without entering that compartment at all. It is the most clinically advanced representative of a small group of anti-lipidemic drugs with this same circumscribed mechanism of action. They are anion exchange resins. Anion exchange resins are antacids, and cholestyramine is one with a particular affinity for bile acids. Cholesterol itself is normally excreted via the digestive tract in the form of the bile acids secreted there by the liver. But the same bile acids are readily absorbed from the intestine, and the rate at which the liver thus eliminates cholesterol depends on the rate of bile-acid reabsorption and recirculation to the

liver. Cholestyramine readily combines with bile acids, forming complexes that cannot be reabsorbed. As a result, bile acid excretion increases. This causes the liver to increase bile-acid production from cholesterol and thus to reduce blood-cholesterol levels.

The taste of cholestyramine alone is bad, and the 6-12 gram daily dosage necessary to lower serum cholesterols much more than 15 percent seemed large in earlier clinical studies. Furthermore, there was little effect on triglycerides at these dosages. But there were no toxic effects, and this, plus ingenuity in disguising the taste, has since encouraged even larger doses in the range of 20-25 grams--still without toxic effects through continuous periods as long as 18 months in at least one group of patients. In this group serum cholesterols dropped an average of 43%, triglycerides 55%, and phospholipids 25%. The profound effect on the triglyceride fraction is both surprising and exciting; especially since the drug is so free of toxic effects and apparently does not require onerous dietary restrictions. Cholestyramine seems to be moving toward the forefront of the most promising of the antilipidemic drugs.

Neomycin and certain other antibiotics, when given orally, have brought about reductions in blood cholesterol comparable to those achieved with diet therapy. These drugs apparently increase the excretion of bile acids, causing additional cholesterol to be diverted for bile acid production by the liver. The drugs may act by killing off normal intestinal bacteria which play a part in normal bile acid metabolism, although this has not been precisely determined. More recent evidence indicates Neomycin also forms chemical complexes with the bile acids, and so may act in a manner similar to cholestyramine. Diarrhea has been a common side effect, though seldom a serious one.

Combinations of two or more drugs with different mechanisms of action in the same dosage schedule may offer additional advantages without proportionally disadvantagious side effects. Nicotinic acid in combination with d-thyroxine, cholestyramine with d-thyroxine, and CPIB with d-thyroxine or androsterone have been tried with some success in various patient groups. The combination of CPIB and d-thyroxine, for example, was more effective (20% average reduction) than either d-thyroxine (14%) or CPIB (12%) alone for reducing serum cholesterol levels.

To summarize: At present, both dietary manipulation and certain drugs and hormones have proved feasible for reducing elevated blood cholesterol levels, although none of these will work in all cases, nor are any of them as effective against severe hypercholesterolemia as one might wish. Considerably less is known about factors affecting blood triglyceride levels and about measures for controlling hypertriglyceridemia, a condition which also appears to increase coronary heart disease risk. And it remains to be proven conclusively that lowering blood lipid levels by any means--drugs or diet--affects incidence or mortality rates in coronary heart disease.

Information relating to this question should be forthcoming from their Coronary Drug Project. The largest clinical trial of its kind, the development of the Coronary Drug Project began in 1960 at the initiative of the National Advisory Heart Council. After operational and other details had been worked out, the clinical phase of the project was begun at four centers in April 1965; and by summer 1967, all 55 participating medical centers had been enrolled. The project will require approximately 8,500 patients to demonstrate unequivocally a 25% or greater mortality decrease in drug-treated patients. Each center is expected to recruit about 150-160 patients toward this total.

Patients eligible for the Coronary Drug Project are males, aged 30 through 64, who have had one or more documented myocardial infarctions, who are free of other life-threatening diseases, and who live within a reasonable distance of one of the study centers.

Drugs being evaluated by the Coronary Drug Project are four agents previously shown to reduce blood lipid levels and to be free of serious toxicity. They are:

1. Conjugated equine estrogens in two dosage schedules
2. Dextrothyroxine
3. Ethyl chlorophenoxyisobutyrate (CPIB)
4. Nicotinic acid

Subjects under treatment with these agents will be compared with a control group which also will receive standard medical care but will not receive these drugs. All subjects will be followed for five years to determine the effectiveness of these agents in reducing plasma levels of cholesterol, triglycerides, and phospholipids and to evaluate the resultant effect (if any) of reduced lipid levels on heart disease mortality.

In human terms, if the effectiveness of these drugs is, in fact, related to their ability to lower the blood fats, it can be calculated that such drugs might be able to reduce the number of recurrent heart attacks by 30 percent. This would have obvious and important consequences for the five million or more Americans who have coronary heart disease. Furthermore, demonstration of the principle that drugs which lower blood lipids can improve survival would stimulate the development of still more satisfactory lipid-lowering drugs for the treatment and prevention of coronary heart disease.

The participating institutions are concentrated mostly in populous regions. They range from large medical centers to small clinics, and also include private and community hospitals, Veterans Administration hospitals, and Public Health Service hospitals. Virtually all regions of the United States are included.

Elevated Blood Pressure. Risk of coronary heart disease increases in step with increasing blood pressure. This gradient of risk appears to apply even in the so-called "normal" blood pressure range. Elevated blood pressure is especially serious if it is accompanied by elevated blood-lipid levels, since there is abundant evidence that hypertension hastens the deposition of cholesterol and other lipids in the blood vessel wall. Fortunately, the physician today is armed with a variety of effective drugs for controlling blood pressure in hypertension of all degrees of severity, including mild hypertension all too often left untreated previously. Further, many of these drugs are easy to handle clinically and are largely free of the undesirable side effects of earlier therapeutic measures.

Mild sedatives, such as phenobarbital or meprobamate may provide adequate blood-pressure control in cases of very mild hypertension, especially if the patient is high-strung or subjected to excessive pressure and tension in his job or family relationships.

Reserpine and certain of its analogs, such as syrosingopine, are usually effective against mild to moderate hypertension, especially when used in combination with diuretics. Reserpine reduces sympathetic nervous activity by knocking out the mechanisms that maintain norepinephrine stores at sympathetic nerve terminals. Norepinephrine is the chemical transmitter released by sympathetic nerve impulses to convey their messages to target organs. By reducing the concentrations of norepinephrine in these terminal stores, reserpine and its analogs reduce the intensity of sympathetic traffic calling for blood vessel constriction.

Methyl dopa is a recent addition to the physician's arsenal of drugs effective against moderate to severe hypertension. The drug is taken up by sympathetic nerve terminals and converted to alpha-methyl-norepinephrine, which replaces much of the norepinephrine in the terminal storage site. Like norepinephrine, alpha-methyl-norepinephrine is released by sympathetic stimuli; but it has a much weaker action on receptors in the blood vessel wall, thus reducing the intensity of the blood-vessel response to such stimuli. The drug also produces mild tranquilizing effects through some action on the central nervous system, but whether this action contributes to its blood pressure effects is not known.

In long-term clinical trials at NHI, methyl dopa has effectively controlled blood pressure in about two-thirds of hypertensive patients in which it has been tried. Its performance has been especially impressive against severe hypertension, including the malignant phase of the disease. It is easy to handle clinically, mixes well with other hypotensive agents, and produces few untoward side effects.

Pargyline, another effective new drug, belongs to a class of compounds called monoamine oxidase inhibitors. Some earlier MAO inhibitors tested by NHI scientists were effective agents for lowering blood pressure, but proved so toxic that the future of MAO inhibitors as an approach to hypertension therapy seemed bleak indeed.

Subsequent studies revealed that the fault lay, not in the inhibition of monoamine oxidase, but in the fact these earlier inhibitors were all chemical derivatives of hydrazine, a highly toxic substance that can cause damage to the brain and other tissues.

Pargyline is a new breed of MAO inhibitor. It is not a hydrazine derivative, but it combines high potency as an MAO inhibitor and hypotensive agent with low toxicity. It is highly effective against moderate to severe hypertension in most instances. Unlike most hypotensive agents, which usually produce mild sedation and tranquilizing effects, pargyline is a mild central-nervous-system stimulant or antidepressant.

Guanethidine is an extremely potent hypotensive agent that is highly specific in its action. Like reserpine and methyl dopa, guanethidine reduces sympathetic activity by impeding nerve-impulse transmission between peripheral sympathetic nerve terminals and their target organs. Unlike reserpine and certain other hypotensive agents, guanethidine does not act centrally to produce sedation and tranquilizing effects because it cannot readily penetrate the blood-brain barrier. Guanethidine also differs from these other agents in that norepinephrine depletion does not appear to be the key to its hypotensive action. Guanethidine appears to release norepinephrine from nerve terminal stores by persistent activation of the same mechanism through which nerve impulses liberate the amine. While this action can eventually deplete sympathetic terminals of norepinephrine, effective nerve blockade is produced long before this happens. The blockade may result from a persistent depolarization induced by the drug's unrestrained release of norepinephrine.

Ganglionic blocking agents 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, and their use is often attended by undesirable side effects, such as constipation, dry mouth, and sexual impotence. However, very frequently, blood pressure can be controlled by using ganglionic blocking agents in combination with thiazide diuretics and various other hypotensive agents previously described. Such measures combine the hypotensive action of numerous agents while reducing the intensity of the side effects produced by any of them.

Diuretic drugs, which increase salt and water excretion by the kidneys, are used to combat fluid retention in congestive heart failure and other clinical states causing edema. Certain diuretics also reduce blood pressure and potentiate the effects of other antihypertensive drugs. Previously, the blood pressure effects of diuretics had been attributed primarily to the reduction in circulating plasma volume resulting from drug-induced water losses. However, NHI grantees report that salt excretion rather than water excretion appears to be the key to the blood pressure effects of furosemide and thiazide diuretics. Two to six hours after either drug was given intravenously to patients, their blood pressure fell by an average

of 16 millimeters of mercury. This was accompanied by a sharp decrease in plasma sodium concentrations and by an average reduction of 500 milliliters (about a pint) in circulating plasma volume. Maintenance or restoration of normal plasma volume with infusions of Dextran (a plasma substitute) did not affect the hypotensive action of either diuretic. Infusions of saline, given when the diuretics were administered, did not prevent the drug-induced reduction of plasma volume, but prevented any reduction in blood pressure. When saline infusions were given after the hypotensive effects of the diuretic had developed, they caused no rise in blood pressure while the drug-induced sodium deficiency persisted. But when positive sodium balance was restored, blood pressure promptly climbed to pretreatment levels.

Catapres, a new drug from Geigy laboratories, appears to be a potent agent for reducing blood pressure in hypertension. NHI grantees report that oral doses of only 450-500 micrograms a day (a microgram is one millionth of a gram) reduced blood pressure by 20 points or to normotensive levels in 6 of 16 hypertensive patients. When Catapres was supplemented with thiazide diuretics, similar degrees of blood-pressure control were achieved in 12 of 13 patients. The side effects noted were drowsiness and dryness of the mouth.

Intensive studies were carried out in patients receiving 300-750 micrograms of Catapres. Maximum blood pressure effects occurred after 1-2½ hours, when standing blood pressure fell by an average of 38 points, supine blood pressure by 35 points. The hypotensive effects were accompanied by reductions in cardiac output, peripheral blood vessel resistance, and kidney bloodflow.

Catapres, developed in Europe, was intended for use as a nasal decongestant until it was discovered that, on a weight basis, it was the most powerful hypotensive drug of all. The grantees feel that this drug shows promise in the clinical management of ambulatory hypertensive patients.

Another very new compound which may deserve mention is a phospholipid, recently isolated from kidney tissue, which completely inhibits the blood vessel response to renin and reduces blood pressure in animals with induced renal hypertension. It has proven effective against the renin of all species tested. When injected into rats with acute or chronic renal hypertension, 8-15 milligrams of this phospholipid per kilogram of body weight reduced blood pressure by as much as 130 points. When injections were discontinued, blood pressures promptly returned to pretreatment levels. The phospholipid had no effect on blood pressure in normal animals. This compound appears to be a specific inhibitor of renin, and may thereby be a tremendously important find if this is confirmed in further studies. It does not prevent the rise in blood pressure ordinarily produced by infusions of angiotensin. The work is thus far preliminary, but the scientists are currently working out the chemical structure of this phospholipid and seeking to confirm its mechanism of action.

Coronary Heart Disease: Clinical Management

A new family of drugs proving highly effective in the clinical management of angina pectoris are the beta adrenergic blocking agents. These drugs selectively block those receptors in the sympathetic nervous system that normally increase heart rate and heart work in response to exertion or stress. By curbing these increases, beta blocking agents such as propranolol substantially increase the exercise tolerance of angina sufferers. Used alone or in combination with nitroglycerine, the beta blockers have often enabled such patients to resume activities that formerly would have brought on disabling chest pain.

A study involving propranolol just published shows that the short-term outlook for survival and recovery of coronary patients with angina is also definitely improved by this beta adrenergic blocking agent. These findings are based on a 2-year review of 135 patients with angina and coronary disease verified by x-ray visualization. The control group consisted of 43 patients receiving standard medical therapy, including nitroglycerine and related agents for relief of chest pain. In this group there were 6 deaths, 5 heart attacks, and a 56.8 percent incidence of congestive heart failure. Among 55 propranolol-treated patients, there was only one death, 3 heart attacks, and a 35.8 percent incidence of congestive heart failure. Interest in this and other beta blocking agents has quickened noticeably throughout the medical community during recent months.

Acute heart attacks (myocardial infarctions) usually result from the complete occlusion of coronary arteries by blood clots. These clots may form on atherosclerotic lesions in the coronaries, especially in narrowed segments where the blood flows more slowly; or they may arise in larger vessels elsewhere in the body, break free, and eventually be carried by the blood into the coronary arteries where they become lodged in one of the coronary branches.

Anticoagulant drugs cannot dissolve clots, but they do help to minimize heart damage resulting from the coronary thrombi or emboli described above. By preventing the growth or extension of such clots, anticoagulants may prevent them from completely obstructing a partly occluded vessel, or from sealing off other branches arising near the site of blockade. They help to prevent the formation of additional clots in other coronary branches or in collateral vessels that may be supplying blood to the ischemic area. Anticoagulant therapy also reduces the risk of additional infarction, pulmonary or cerebral embolism, and venous thrombosis, which may complicate the acute phase of myocardial infarction.

Anticoagulant therapy has its complications and its critics. But available clinical evidence overwhelmingly favors the use of anticoagulants during the acute phase of heart attacks. In most clinical studies,

these drugs have increased survival anywhere from 30 percent up to more than 50 percent. When patients have been carefully screened to exclude those with disorders that would increase the hazards of anticoagulant therapy and when therapy has been closely and properly supervised, there have been few serious bleeding episodes or other complications attributable to anticoagulant therapy.

There is also a preponderance of clinical evidence that the risk of recurrent heart attacks is reduced and long-term survival increased by keeping patients on continuous anticoagulant therapy during the first year or two after their attacks. To date, however, there have been too few long-term studies to establish conclusively whether the degree of protection conferred by anticoagulants beyond this period is sufficient to justify the risk, inconvenience, and expense of continuing this treatment indefinitely.

Fibrinolytic agents, which bring about the dissolution of blood clots--either by attacking them directly or by activating the body's own clot-lysing mechanisms--may well turn out to be even more effective than anticoagulants in reducing mortality among heart-attack victims. At present, however, this is theory; for the value of fibrinolytic therapy in the clinical management of coronary thrombosis has still not been fully proven.

A number of investigators have employed various fibrinolytic preparations in the clinical treatment of heart attacks. Many of their results have indicated that fibrinolytic therapy reduced the extent of heart muscle damage, improved the clinical course, and increased survival among these patients. But the validity of these findings has been open to dispute. Many of these studies were not adequately controlled and involved too few patients to justify strong statements concerning the worth of fibrinolytic therapy. Further, lacking reliable, objective techniques for determining the extent of clot dissolution brought about by these drugs and for assessing the resultant effects on coronary blood flow and heart-muscle salvage, investigators have had to rely heavily upon clinical impressions. The clinical course of myocardial infarction is too notoriously variable to inspire confidence in such impressions.

Further undermining confidence in the results of earlier clinical studies was the lack of suitably purified fibrinolytic preparations. Wide variations in potency between different batches of the same preparations created problems in establishing dosage schedules, and these problems were compounded by wide variations in response to these preparations among patients.

A number of the difficulties that had hampered clinical progress in this field have now been overcome, and more definite clinical studies have become feasible. The fibrinolytic agent of choice is now urokinase, derived from human urine. Urokinase is a "native" substance. Being

non-antigenic, it has distinct advantages over earlier fibrinolytic agents (streptokinase, staphylokinase) derived from bacteria. Anyone who has ever had a streptococcal or staphylococcal infection has developed antibodies against streptokinase or staphylokinase. Thus, in using these agents, the dosage must be increased sufficiently to neutralize the antibodies and still have enough activator left over to bring about clot dissolution. The intense antibody response elicited by these agents makes it extremely hazardous to use them more than once. However, preliminary results with urokinase indicate that infusions of this agent can produce intense fibrinolytic activity in the blood without the side effects of earlier fibrinolytic agents.

An NHI project involving carefully controlled clinical studies with highly purified urokinase and standardized methodology is in early stages at five cooperating institutions. The drug is being tested against peripheral vascular thrombosis and pulmonary embolism, but the project will soon be expanded substantially to encompass definitive studies on the value of urokinase against coronary occlusion and certain strokes resulting from clots or emboli.

One study in patients with pulmonary embolism indicates that there are beneficial effects if the symptoms have not been present for more than two weeks. Earlier animal work had indicated that urokinase could achieve near-complete dissolution of clots 7 days old and partial dissolution of 14-day-old clots. Clots older than this were resistant to attack by the drug. In the recent study, urokinase was tested in 10 patients with pulmonary embolism documented by x-ray arteriography. In 3 of these patients, symptoms had occurred within 2 weeks of urokinase therapy. All 3 patients exhibited marked relief of symptoms, improvement of lung function, and arteriographic evidence of clot dissolution. Another 3 of these patients had experienced the symptoms for more than 2 weeks, but also had evidence of fresh embolism superimposed on their pre-existing condition. In these patients, urokinase therapy produced some relief of symptoms, but lung function improved only slightly. Three other patients had histories indicative of months to years of recurring embolism and only slight worsening of symptoms with two weeks of urokinase therapy. In these patients, therapy produced no detectable improvement. The tenth patient had acute symptoms, but these proved to be due to an old organized clot. The patient, in shock when urokinase was administered, showed no improvement and subsequently died. The clinical results support the findings of the earlier animal studies: urokinase accelerates the dissolution of fresh clots, but not of "old" ones.

Death from a heart attack is due to one or more of three mechanisms. Most commonly the death-dealing mechanism is an abnormal, chaotic rhythm of the heart or an actual arrest of cardiac contractions. Cardiac defibrillators, external electrical pace-making and driving devices have already proven life-saving in many instances by returning the heart

rhythm to normal. Drug control of cardiac rhythmicity is another avenue of research holding great promise for preventing or controlling the rhythm complications of myocardial infarction.

The second mechanism of death in acute myocardial infarction is a profound derangement of the nerve reflexes which integrate heart function with general body physiology. The often fatal systemic circulatory collapse, or "shock," which results from this reflex disturbance is little understood and its clinical management is largely empirical. But drugs for controlling such shock are under intensive study.

Antiarrhythmic drugs are used to correct variations from the normal rhythm of heart beat. Arrhythmias upset the smooth contraction sequence of the heart, often compromise its pumping efficiency, and may progress to cardiac arrest. They are a dreaded complication of heart attacks and are often the immediate cause of death among heart-attack victims.

Fortunately, if promptly detected and treated, many arrhythmias stemming from heart attacks can be corrected or controlled by drugs such as digitalis, quinidine, diphenylhydantoin, procaine amide, isoproterenol, and others. Serious arrhythmias that fail to respond to drug therapy can often be corrected by precisely timed shocks delivered by the heart by electrical defibrillation equipment.

The local anesthetic lidocaine now appears to be a safe and effective agent for treating and preventing ventricular arrhythmias in patients who have experienced acute myocardial infarctions. Earlier surgical studies had indicated that lidocaine reduced heart-muscle irritability after open heart surgery and effectively curbed ventricular arrhythmias during postoperative period. In the currently reported studies, lidocaine was used in 21 patients with ventricular arrhythmias following heart attacks. Each received a dose of 25-100 milligrams, then was maintained by intravenous infusions of 0.5-4 milligrams per minute for periods of up to 72 hours. Excessive ventricular rates were thus controlled in 20 instances and the frequency of premature contractions was reduced in 17 of the 21 patients.

The quest for new and better antiarrhythmic drugs continues, as does basic research to define more precisely the mechanisms of action, the advantages, and the limitations of currently available drugs. Knowledge gained from such studies is enabling the physician confronted with a particular type of arrhythmia to choose from among a fairly wide selection of agents the drug or combination of drugs most likely to be effective in coping with the problem.

Vasopressor drugs are often lifesaving in cardiogenic shock, an extremely dangerous complication of heart attacks which formerly carried mortality rates ranging from 80-95 percent. Improved therapeutic measures have reduced this appalling toll, though mortality has continued to range from 35-60 percent.

Often, an important factor in cardiogenic shock is extensive heart muscle damage sustained as a result of the attack, which may severely compromise the pumping effectiveness of the heart. Frequently, heart output is further diminished by the loss of blood-vessel tone. Widespread relaxation of blood vessels increases the capacity of the peripheral vascular system, especially the venous bed, and thus reduces the amount of blood returning to the heart.

When both of these factors are operative in cardiogenic shock, the drugs most frequently used are norepinephrine, metaraminol, or mephenetermine. These agents act directly on the heart to improve its pumping performance and to increase its output, and they also increase blood-vessel tone. This dual action tends to raise systemic blood pressure and to increase effective bloodflow to the organs and tissues of the body.

One study compared the effects of two drugs--norepinephrine and isoproterenol--in 13 patients in cardiogenic shock. Both drugs are powerful heart stimulants; but norepinephrine also acts to raise blood pressure by constricting the smallest arteries, whereas isoproterenol dilates them. Each patient received first one, then the other drug. His response to each was evaluated in terms of average pretreatment values of heart output, arterial and venous blood pressure, and peripheral vascular resistance. Norepinephrine increased heart output by 15 percent and mean arterial pressure by 55 percent. During the period of increased arterial pressure, the patients' urinary output increased and general clinical condition improved. Isoproterenol increased heart output by 25 percent, but arterial pressure fell slightly as a result of a decrease in peripheral vascular resistance. No clinical improvement was observed during isoproterenol infusions. Moreover, when 4 patients were switched from norepinephrine to isoproterenol, their clinical condition deteriorated markedly within minutes, with fatal results in 3 patients.

Other drugs, such as methoxamine, phenylephrine, and angiotensin, also increase blood-vessel tone; but their effectiveness in cardiogenic shock is limited by the fact that they have no direct effect upon the heart. Thus, while blood pressure may be raised by these drugs, heart output and systemic blood flow may actually decrease.

In other instances of cardiogenic shock, there may be widespread blood vessel constriction rather than relaxation. This may sharply reduce heart output and systemic blood flow by forcing the damaged heart to pump against a higher resistance. In such instances, vasopressor drugs that increase blood vessel tone may only make the situation worse.

Recently, NHI grantees tested several treatment regimens in animals with heart attacks induced by injecting plastic spheres into the coronary circulation. Of animals developing cardiogenic shock, 85 percent died within 24 hours if untreated. But 75 percent survived when treated with infusions of low-molecular-weight dextran, a plasma expander, plus phenoxybenzamine, a drug that selectively blocks nerve receptors that mediate blood vessel constriction. By increasing circulating blood volume and decreasing blood vessel resistance, the combination boosted heart output and effective systemic bloodflow. It has since been used, with similar gratifying results, in selected patients with cardiogenic shock.

Norepinephrine increases heart rate and the vigor of heart muscle contraction by stimulating beta receptors of the sympathetic nervous system. But this drug also stimulates sympathetic alpha receptors. Alpha adrenergic stimulation causes blood vessel constriction that reduces the overall effect of norepinephrine on cardiac output and coronary bloodflow while increasing the cardiac workload. NHI grantees report that using norepinephrine to augment cardiac output plus phentolamine to achieve partial blockade of alpha receptors increased coronary bloodflow by as much as five times without significantly increasing the workload on the heart in animals with induced cardiogenic shock.

Dopamine, the chemical precursor of norepinephrine, is a potent beta adrenergic stimulating agent that also dilates the blood vessels of the kidney. Preliminary studies by NHI grantees indicated that infusions of dopamine lasting up to 35 minutes increased heart output and decreased peripheral blood-vessel constriction in 7 patients with hypotension, 3 of them in clinical shock.

Subsequently, the drug was infused for periods of 2-51 hours in 14 other patients with severe hypotension and reduced kidney function due to heart disease. Both peripheral bloodflow and urinary output improved markedly in 7 patients, while one or the other function was improved in 6 others. The grantees suggest that dopamine may prove superior to certain other vasopressor drugs in the clinical management of shock of cardiac origin.

Chronic congestive heart failure may develop as a consequence of a long-standing circulatory disorder, such as hypertension, that places a prolonged heavy burden on the heart, or it may stem from the loss of functioning heart muscle as a result of one or more heart attacks. Whatever the cause, the failing heart is incapable of coping with the circulatory demands of the body. Heart failure is commonly attended by abnormal salt retention and the accumulation of fluid in the lungs (pulmonary edema) can be a life-threatening complication. Treatment of congestive heart failure entails reducing the workload on the heart; using cardiac stimulants to improve its pumping efficiency and output, and preventing or eliminating edema.

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Digitalis, used against congestive heart failure since 1785, is still the drug of choice, although crude digitalis preparations have been supplanted by digitoxin and digoxin, purified active ingredients of digitalis plants.

In patients with congestive heart failure, digitalis slows heart rate, but increases the vigor and efficiency of heart muscle contraction so that more blood is expelled per beat. In normal subjects, digitalis increases heart output only slightly, because the drug causes blood-vessel constriction that largely negates its cardiac stimulant effects by forcing the heart to work against a higher resistance. However, for reasons that are not clear, this blood-vessel constriction does not occur in patients with failing hearts treated with digitalis, so that the drug substantially augments heart output and systemic bloodflow.

NHI grantees have just reported a simple, reliable method of ascertaining proper maintenance doses of digitalis in heart failure patients with impaired kidney function or in patients with altered renal function following surgery. The dosage required to maintain body stores of digitalis must balance losses of the drug via kidney excretion. These scientists have found that maintenance doses can readily be calculated on the basis of a simple, routinely performed test of kidney function called the creatinine clearance test. The test is ordinarily employed to measure the rate at which blood plasma is filtered by the kidney, but these investigators found that the rate at which the kidney removes creatinine from the plasma is directly proportional to the rate at which it removes digitalis. Hence, from creatinine clearance rates, which can be determined simply and quickly, the half-life of digitalis can be calculated and the appropriate dosage of the drug determined to hold body stores constant.

Digitalis and a low sodium diet may provide adequate control of edema in many patients with congestive heart failure; but, should edema be severe or refractory, the physician has at his disposal a wide variety of clinically proven diuretic agents from which to select the one best suited to the needs of the individual patient.

Although these agents may differ in mode or site of action, potency, onset and duration of action, and route of administration, diuretic drugs promote the elimination of excess fluid primarily by increasing urinary excretion. Most also increase urinary loss of both potassium and sodium so that patients on diuretic therapy are usually given potassium chloride supplements to prevent potentially dangerous deficits. In a number of preparations, the potassium supplement is incorporated into the diuretic capsule.

Organomercurial agents were among the earliest diuretic agents. Usually given by injection, though some are suitable for oral use, they are extremely potent, fast-acting drugs employed primarily in clinical situations requiring that the patient be rid of a lot of water in a hurry, such as severe pulmonary edema.

Chlorothiazide, developed by Merck, Sharp and Dohme in 1955 and introduced commercially in 1958, is the most widely used diuretic. It is an oral agent well suited for long-term control of edema. Its diuretic action is most pronounced in severe edema, then usually diminishes as the edema clears, thereby reducing the threat of fluid and electrolyte imbalances. The drug is also widely used in the treatment of hypertension, since it has a mild hypotensive action and also potentiates the effects of a number of other blood-pressure-lowering drugs. Chlorothiazide has spawned a large number of thiazide derivatives, each a more potent diuretic than the thiazide that preceded it. But these derivatives provide few clinical advantages over chlorothiazide other than requiring smaller doses to achieve the same clinical result.

Triamterene, a diuretic recently introduced by Smith, Kline and French, is reportedly highly useful in the treatment of edema due to congestive heart failure and/or excessive production of aldosterone, a hormone that promotes sodium retention by the kidney. This drug also promotes the excretion of sodium without causing undue potassium losses, a distinct advantage over the thiazide diuretics.

Ethacrynic acid introduced by Merck, Sharp and Dohme is a new, orally administered agent that, in speed and potency of action, rivals the organomercurial agents. In clinical trials it has proved extremely useful in the clinical management of severe edema, especially life-threatening pulmonary edema, and has often proved effective against edema refractory to other diuretics.

Aldosterone Antagonists, such as spironolactone, are steroids that counter the salt-retaining action of aldosterone. They are expensive, and their clinical value is limited to those relatively rare clinical situations where excessive aldosterone production is directly responsible for the edema or else is a significant aggravating factor.

## Conclusion

Heart damage due to atherosclerosis is typically a late, often unexpected, largely irreversible consequence of a slowly progressive condition initially acquired in early life, possibly in childhood or early adulthood. The greatest hope for effectively combatting this massive and growing health problem resides in identifying and eliminating primary and antecedent causes, so that attempts to halt or reverse the secondary and multiplied consequences in patients may ultimately be unnecessary. Meanwhile, the essential pursuit of more effective means for treating patients already victimized by coronary heart disease is yielding abundant practical results.

The Coronary Drug Study, previously described, is an example of a targeted research program concerned primarily with the prevention of recurrent

heart attacks. But, if these drugs confer significant degrees of protection in patients with clinically manifest heart disease, their benefits are likely to be even greater among subjects who are coronary prone but who have not yet experienced clinical complications.

The salvage and rehabilitation of patients who have already sustained heart attacks is the goal of the Institute's Artificial Heart-Myocardial Infarction Program. While the bioengineering component is driving toward the development of effective, reliable devices to provide temporary or permanent circulatory assistance to damaged or failing hearts, and, if developments warrant it, a total replacement for hearts damaged beyond salvage, the medical component will direct a program of intensive biomedical research on the acute heart attack and its medical management. The goals of the medical program are to learn more about acute heart attacks, their presently unpredictable clinical course, and the mechanisms underlying potentially lethal complications such as arrhythmias and shock. It will seek improved techniques for diagnosis and for the evaluation of irreversible heart muscle damage, devise and evaluate methods for the continuous monitoring of patients, develop and test new drugs and therapeutic procedures, and define the place of heart-assist devices in the clinical management of heart attacks. The ultimate goal is to reduce the necessity for heart assist devices by providing less drastic, equally effective therapeutic alternatives.

The achievements of these realistic goals could have a dramatic impact on our presently appalling death rate from coronary heart disease and its complications.

CARDIOVASCULAR RESEARCH AND TRAINING CENTERS

Mr. FLOOD. You have a relatively new program of specialized cardiovascular research and training centers.

Dr. FREDRICKSON. Yes, sir.

Mr. FLOOD. I want you tell us what they are, where they are, how many there are, their present cost, and future plans for them.

Dr. FREDRICKSON. Yes, sir.

The specialized cardiovascular research and training centers that appear in this line item are, in the first instance, one of the Institute's major responses to its responsibilities in relationship to the heart, cancer and stroke activities.

The aim of this program, succinctly put, is to establish about this country centers of excellence, using mostly centers that we now have but to add to those centers such resources as are needed to provide facilities for high-grade research and clinical care and the training of individuals involved in these areas by bringing together many disciplines. Cardiology today is a very rapidly changing specialty. It is quite susceptible to changes in engineering and computer technology, as well as the basic sciences, and we have to get these people together. They think together, they criticize each other together, and research and training moves forward better in that kind of consolidated environment.

At the present time, sir; we have funds only for planning these centers. The $800,000 in the current appropriation is for the planning.

Mr. FLOOD. Suppose you have 10 centers. How would you determine their geographic distribution?

Dr. FREDRICKSON. Our aim, through these planning grants, is to allow institutions to identify themselves and we to identify those that have the potential of developing this kind of center of excellence.

We give them the support to bring in consultants and to think, and for such resources as are needed to plan the organization, and then we will work with them in the development within their institution of this type of organization.

Mr. FLOOD. What is a ball park figure on costs?

Dr. FREDRICKSON. A ball park figure for a center of this sort is about $4 million per year.

Mr. FLOOD. What about the initial investment?

Dr. FREDRICKSON. The initial investment in a few places may go up to as much as $4 million in construction costs. There are places where no construction will be required.

Mr. FLOOD. Construction?

Dr. FREDRICKSON. Yes.

Mr. FLOOD. What about hardware?

Dr. FREDRICKSON. Early implementation of resources would fall into the area of perhaps another million in addition to $4 million operating costs, but we can gradually move into this level.

Mr. FLOOD. Is there any possibility of a bottleneck in your hardware?

Dr. FREDRICKSON. It is available, sir; and many of these institutions have some of that hardware already. We want to get it into a spot where it can be used as efficiently as possible.

LABORATORY AND CLINICAL RESEARCH

Mr. FLOOD. You are asking for an increase of $475,000 for laboratory and clinical research. What is that for?

Dr. SHANNON. That is for the direct operation at Bethesda.

Mr. FLOOD. You know very well, Doctor, that all budgets are vulnerable this year. If you do not get these additional positions, how seriously will it affect your program?

Dr. SHANNON. If the dollars and positions are not available, it will block off some of the planned development of the artificial heart-myocardial insufficiency program. It will further curtail the number of research grants that can be supported. It will curtain the direct operation in Bethesda in some of its essentials.

We are starting off with a budget that already constitutes a small, but nonetheless substantive, cut in program. If the dollars that it would provide merely to meet the cost-of-living increase are not provided, there will indeed be a cut in the substance of what can be done. The specific things that would suffer would be the artficial heart, the grant program, and the direct operation.

PREVENTION OF HEART ATTACKS

Mr. FLOOD. What research are you conducting on prevention of heart attacks?

Dr. FREDRICKSON. That is the nature of some of these studies related to drugs and to diets in the first instance. It is very interesting and very important, Mr. Chairman, that we have, along with Finland, the highest rate of heart attacks in men between the ages of 35 and 65 in the world.

A country like Sweden, which is a highly industrialized society, just about like our own, has an attack rate just half of that.

One of the major questions in the field of prevention is to find out why this is so. We ought to be able to turn coronary deaths in this population of ours down to the Swedish rate. If we did we would save about 100,000 lives per year in men below age 65. This is our most serious challenge and our No. 1 priority goal.

ARTIFICIAL HEARTS

Mr. FLOOD. I have read in the last week where two researchers have come up with a new type of artificial heart, too large to be inserted now. Have you read that story?

Dr. FREDRICKSON. I am not sure which one that is. I probably have seen it.

Mr. FLOOD. What research are you doing in this area?

Dr. FREDRICKSON. Our artificial heart program, Mr. Chairman, is concerned primarily with the immediate problem of temporary salvage.

Most of our budget, probably nine-tenths of the artificial heart program budget, is devoted to the development of pumps that will assist the heart for short times because we believe we can actually tide people over acute heart failure and probably salvage a great many individuals.

Mr. FLOOD. What about miniaturization of the hardware?

Dr. FREDRICKSON. That is proceeding in certain instances.

We also have a much smaller part of the program dedicated to miniaturization of the material. Also, miniaturization will be important in some of the assist devices. Perhaps many of them may be permanently implanted to permanently assist the heart without taking over its full load.

COST OF HEART TRANSPLANT PROGRAM

Mr. FLOOD. Dr. Shannon, we discussed heart transplants at some length during your testimony.

Are there any observations you think it might be appropriate for Dr. Frederickson to make on the same subject? We said a good deal.

Dr. SHANNON. Yes; I think there is one factor we did not discuss.

I was talking to Dr. Fredrickson after the testimony and said he might expect some questions in this and should be prepared to be quite specific. I think you would be interested if Dr. Fredrickson told you some of the cost estimates that have been made on the basis of the work to date.

One is startled by the figures. It takes about $10,000 a year for hemadialysis with an artificial kidney per patient. Dr. Fredrickson has specific facts on the cost of these operational procedures at the present time that I think you would be interested to hear.

Dr. FREDRICKSON. The cost of a heart transplant at present rates, which is based on relatively little experience to be sure, is something on the order of $30,000 for the initial expense, and postoperative costs can be run up to $1,000 a day for a number of days.

I think one should at this time assume it will cost about $50,000 to transplant a heart. In this country today there die 150,000 or 160,000 potential candidates for heart transplant under 65 years of age. Many of these patients would never be ideal recipients, some of them die too soon to even enter the hospital.

If we come down to the very bottom figure of 10,000 individuals under 65 alone per year, if you multiply this by a figure of $50,000, which is the bare costs, you come up with a half a billion dollars a year this would amount to. This is certainly the minimum.

The cost of reestablishing or regrafting, replacement of hearts that fail, all the other costs, not amortizing the cost of development, would bring this to several billion dollars a year if this were the only way we have of solving the problem of premature death.

HEART COOPERATIVE DRUG STUDY

Mr. FLOOD. Have you told us enough about the heart cooperative drug study. You know this committee more or less gave birth to that a few years ago. You mention it in your direct statement, but you may wish to add to that in the record as well if you feel you treated it too briefly in your original statement.

Dr. FREDRICKSON. All right, sir.

(The information follows:)

NATIONAL COOPERATIVE CORONARY DRUG STUDY

Coronary heart disease and its complications accounted for approximately 560,000 of the 1 million deaths caused by all cardiovascular diseases during 1965.

Strong epidemiological evidence indicates that elevated blood levels of certain fatty substances, notably cholesterol, are consistently related to increased risk of developing coronary heart disease and its most common manifestation: the heart attack. It seems reasonable to suppose that (1) elevated blood lipid levels also affect prospects for long-term survival after recovery from a heart attack; and (2) drugs that produce sustained lowering of blood lipids should improve longevity among heart attack patients.

This is the principal objective of the NHI coronary drug project, a large-scale, cooperative trial involving 55 study clinics throughout the continental United States, Puerto Rico, and Hawaii. During the next 2 years, this study will provide opportunities for some 8,500 men who have sustained one or more heart attacks to participate in a 5-year trial of four lipid-lowering drugs. The goal is to determine whether one or more of these drugs will reduce by 25 percent or more the 5-year mortality rate among treated patients.

Various studies have indicated that the cumulative 5-year mortality rate among recovered heart attack patients is 30 percent or more. The coronary drug project hopes to pare this mortality rate to 22 percent or less in one or more of the treatment groups by reducing the threat of recurrent heart attacks and other complications in patients with preexisting coronary heart disease.

Secondary objectives of the project are: (1) To evaluate the relationship, if any, between the effects of the drugs on blood lipids and their effects on morbidity and mortality rates; and (2) by studying the control group as intensively as the treatment groups, to gain further information about the long-term outlook for heart attack survivors.

The drugs being evaluated are four agents previously shown to reduce blood lipid levels and to be free of serious toxicity. They are conjugated equine estrogens (at two dosage schedules), dextrothyroxine, clofibrate, and nicotinic acid. All drugs have been released for physician use by the Food and Drug Administration, which has also approved the indications for which they are being studied in the coronary drug project.

The development of the coronary drug project began in 1960 at the initiative of the National Advisory Heart Council. Between 1960 and 1965, a policy board, steering committee, coordinating center, and central laboratory were established; the study protocol was developed; and operational details were worked out.

The first four study clinics were enrolled in April 1965. Clinic enrollment was completed during the summer of 1967 and patient recruitment is well underway. Each clinic is expected to recruit 150 to 160 patients toward the 8,500 total required to insure the validity of the study findings. As of March 1, 1968, approximately 4,400 patients were undergoing or had completed preliminary screening and of these 2,962 had been assigned to one of the five treatment regimens or to the control group.

To assist in patient recruitment, the National Heart Institute has mailed 48,000 information packets on the coronary drug project to general practitioners, cardiologists, and internists practicing in areas where study clinics are located.

Patients must be men, aged 30 to 64, who have experienced one or more documented heart attacks. They should be free of other life-threatening diseases and their coronary heart disease should result in no limitations or only slight limitation of physical activity. They should require neither insulin nor anticoagulants at entry into the study, although anticoagulants may be administered if a recurrent heart attack or other medical indications arise during the patient's participation.

Patients must be referred by their physicians or should obtain his consent. Study clinics will establish liaison with referring physicians to keep them fully informed of their patients' progress. The physician retains control and responsibility for the patients medical care in all particulars except those specifically required by the study protocol.

Uniform observations are recorded on each patient and forwarded for review and analysis to a coordinating center at the University of Maryland. Blood-lipid determinations and other biochemical tests are performed in a central laboratory of the heart disease and stroke control program at the National Communicable Disease Center in Atlanta.

The clinical phase of the coronary drug project will be completed in 1974. The total cost is estimated at $38 to $40 million. Hopes are high that its findings may result in a substantial saving of life and improvement in the clinical managment of coronary heart disease.

Moreover, if one or more of these drugs confers substantial benefit to patients who, having previously experienced heart attacks, are at highest risk of death from coronary heart disease, it would indicate the feasibility of similar approaches among persons who have high lipid levels, but who have not yet experienced manifestations of coronary disease.

NATIONAL BLOOD RESOURCE PROGRAM

Mr. FLOOD. What is the dollar size of the contract with the Red Cross under the national blood resource program?

Dr. FREDRICKSON. It is approximately $1 million at the present time.

Mr. FLOOD. What do they contribute?

Dr. FREDRICKSON. They are working on an integrated fractionization system. By integration I mean the attempt to take one unit of blood, one bottle, and to get all of the fractions of that bottle with the least waste possible.

Mr. FLOOD. What is a fraction?

Dr. FREDRICKSON. A fraction means a particular plasma protein or some other component or cell component within the blood.

Mr. FLOOD. Blood can be broken down into various fractions?

Dr. SHANNON. Yes, sir; usefully so and economically so from the standpoint of the economical use of a bottle of blood.

At the present time we are using platelet fractions, white blood fractions, red blood fractions, plasma, gamma globulin as an immunizing agent, and indeed using fractions of gamma globulin for specific immunization agents.

The trouble is that these fractions cannot be made commercially available because the cost of the blood for a single fraction is too high. The system that Dr. Fredrickson is describing to you, in relation to the Red Cross, permits each unit of blood—that is half a liter of blood, about a pint—if this could be processed so that all of the fractions can be separated in storable form, then it becomes commercially feasible.

Mr. FLOOD. You would separate the fractions and store the fractions?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. In the same manner in which you store the whole blood?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Would you supply for the record at this point a more complete statement on the national blood resource program.

(The information follows:)

THE NATIONAL BLOOD RESOURCE PROGRAM

The national blood resource program established in fiscal year 1967 in the National Heart Institute represents the undertaking of an integrated approach to the technological problems involved in blood banking. Headquartered in the National Heart Institute, the program is a cooperative endeavor and its objectives are importantly related to those of other Institutes and divisions of NIH and to other Federal civilian and military and non-Federal agencies.

The major program goals are: (1) to provide through research improved instrumentation, new methods and systems of handling donor blood to make possible the more efficient production, storage, and distribution of blood and blood products; and (2) to survey our Nation's donor blood resources and their utilization in terms of present and foreseeable needs.

Some specific long-term R. & D. goals of the program are:

To devise efficient, highly automated methods for the mass production of plasma and cellular fractions of blood (red cells, white cells, platelets).

To develop improved, high-yield techniques for the large-scale fractiona-

tion of plasma to provide albumin, gamma globulin, blood clotting factors, and other medically important protein fractions.

To study the feasibility of a computerized national or regional daily shelf inventory system for blood and blood products to minimize losses due to outdating, forestall or meet local shortages, and to minimize problems arising from fluctuations in supply and demand.

The past two decades have witnessed rapid advances in the use of blood for therapeutic purposes. Research has yielded important new knowledge of the functions of many of the elements of blood and has provided fractionation techniques for separating various components out of this complex fluid. One blood fraction after another has proved to have therapeutic usefulness: and, increasingly, such specific fractions are replacing transfusions of whole blood or plasma in clinical states caused or complicated by deficiencies of some particular blood component.

Transfusions of whole blood or plasma are indispensable in those clinical situations where shed blood must be replaced or circulating blood volume expanded. By the use of whole blood or plasma in situations where only red cells, or platelets, or some specific protein fraction is called for is not only wasteful, but carries a greater risk of adverse reactions than would the use of the specific fraction needed.

As physicians have become aware of the therapeutic advantages of blood fractions, the clinical demand for them has increased rapidly during recent years and will rise still more rapidly in the future.

As a first step toward meeting the anticipated demand, the national blood resource program awarded a large contract to the American Red Cross during fiscal year 1967 for the development of an integrated fractionation system for the mass production of cellular and protein components from whole blood.

Medically important cellular components include red blood cells and platelets. Red cell suspensions are used to restore the normal oxygen-carrying capacity of the blood in patients with severe anemias and related red-cell deficiencies. Platelets have proved extremely valuable for preventing hemorrhage in patients with leukemia.

Important plasma protein fractions include:

Albumin, for increasing circulating plasma volume in the treatment of hemorrhage, severe burns, and shock.

Gamma globulin, for protection against infectious diseases.

Concentrates of blood clotting factors, such as antihemophilic globulin, for the prevention or control of hemorrhage in hemophilia and related bleeding disorders.

A major source of loss of donor blood is the outdating of whole blood in storage. At present, blood can be stored for no more than 21 days at 4° C., after which it becomes unsafe for transfusion. The plasma can be saved for fractionation, but the cellular components must be discarded. The annual loss of whole blood through outdating is not known with certainty, but is believed to be substantial indeed. The development and evaluation of better chemical preservatives is thus an extremely important program goal.

Preliminary evidence from U.S. Army and other studies indicate that a chemical additive called adenine can significantly extend, perhaps double the shelf life of whole blood. Because of its promise in diminishing whole-blood losses that now occur through outdating, adenine is being extensively investigated by the national blood resource program.

Ten contracts were awarded during fiscal year 1967 to determine the effectiveness of adenine as a preservative, to assess its effects on blood components, to study its distribution and metabolic fate in the body, and to establish the safety of adenine-treated blood and blood products for clinical use.

These were the first undertakings of the program. Now during fiscal year 1968, the national blood resource program will continue support for the adenine studies, which will require additional time for completion. In addition appropriate support will be given to continuation of the Red Cross large-scale blood fractionation program. An important aspect of this is the development and testing of new high-purity antihemophilic factor concentrates. At present, in terms of availability and cost, there is no altogether suitable AHF preparation to meet the needs of hemophilic patients. Concentrated preparations offer the first promise of adequate treatment for the life-threatening hemorrhages which occur in this disease. The possibility also arises that AHF concentrates can be adapted to use as pre-

ventive treatment to enable the hemophiliac to live an entirely normal and productive life.

The program also plans in 1968 to initiate studies to determine the feasibility of a computer based donor blood inventory system. The principal object would be to make possible a more equitable distribution of the blood supply and thus to forestall the development of local shortages due to fluctuations in supply and demand. Among the additional benefits of such a system would be:

Reduction of whole blood losses due to outdating through redistribution of local surpluses.

Closer coordination of civilian and military blood programs.

A means of summoning prospective donors during slack donation periods.

A means of screening and excluding donors who are probable carriers of infectious hepatitis.

A means of locating rare-blood donors within region, who could then be called upon to donate only when the need for a rare blood type arose. This would eliminate most rare blood losses due to outdating.

During fiscal year 1968, the program will support a very important cooperative clinical trial of the clot-dissolving agent, urokinase. This study of the usefulness of urokinase in the treatment of pulmonary embolism is the culmination of 4 years of basic developmental work and may lead to an even more important trial of urokinase as a treatment for coronary heart attack. The study will involve about 15 institutions and 400 subjects. Patients with pulmonary emboli will be studied intensively before, during and after administration of urokinase to determine if this agent will destroy the clots in the lungs.

Other future projects of the program include: (1) automation of cellular component separation; (2) revision and development of large-scale protein fractionation techniques; (3) clinical evaluation of additional blood components; and (4) development of new materials and designs for blood and component containers.

Mr. FLOOD. Mr. Smith?

BLOOD LIPID LEVELS

Mr. SMITH. Blood lipids may be lowered through dietary means as well as by the use of drugs. Is that correct?

Dr. FREDRICKSON. It has been demonstrated, repeatedly and convincingly, that diet has an important effect on blood lipid levels in man—and many other, but not all, animals. The dietary factors that exert a pronounced influence on blood lipid levels are the quantity of fat, the quality—saturated versus unsaturated—of ingested fat, cholesterol in the diet, and carbohydrates. To a lesser extent certain other constituents of the diet—for example, proteins, minerals—may exert an effect on blood lipid levels. During the past 10 years most clinical research has focused upon the quantity and quality of fat and upon dietary cholesterol.

Mr. SMITH. How much of our resources in both money and personnel are being used on one method compared to the other?

Dr. FREDRICKSON. A significant proportion of the Heart Institute's research programs is concerned with the role of diet as a determinant of blood lipid levels and with the study and clinical evaluation of lipid-lowering diets and drugs as potential means of preventing atherosclerosis, retarding its progress, or perhaps reversing the course of the disease.

It is estimated that in fiscal year 1968 the Heart Institute will support 92 projects amounting to approximately $6,250,000 specifically and primarily aimed at evaluating the effects of drugs or diet on blood lipid levels. Grant-supported activities in which such studies are ancillary or secondary objectives are not included in this estimate. Also omitted are projects which deal with the effects of diets or drugs on blood clotting, pathological changes in artery walls, and so forth,

and others that focus on basic tissue or cellular mechanisms; although these studies are quite relevant to current research in the broad area of atherosclerosis, this brief summary deals only with the immediate question of diet and drug effects on blood lipids.

These 92 projects, and $6¼ millions represent about one-fifth of the Heart Institute's grant support in the area of atherosclerosis. Three-quarters of these projects—70—involve drug studies and these account for about two-thirds of the total funds. Of the $4.2 million allocated to grant-supported drug studies, most—$3.8 million—represents support to the 58 project grants in the cooperative study of drugs and coronary heart disease.

It is estimated that 22 projects—totaling approximately $2 million—dealing with the effects of diet modification on blood lipids will be supported this year. Approximately $1¼ million will be for the support of human, clinical studies of diet, and blood lipids.

It is apparent that the average cost of these studies is high, averaging close to $68,000 per grant. This reflects the emphasis on clinical investigations, and their relatively greater costs, as compared with projects devoted to animal studies. The average project involves 1.5 professional scientists and 3.3 supporting personnel. These figures reflect, once again, the emphasis on clinical studies and their relatively higher requirements for personnel.

I will be happy to submit a table summarizing, for fiscal year 1968, estimated Heart Institute grant support for studies of drug and diet effects on blood lipids.

(The table follows:)

| | Number of grants | Number of Personnel | | NHI support |
|---|---|---|---|---|
| | | Professional | Technical and other | |
| Drug studies: | | | | |
| Clincial | 66 | 93 | 179 | $4,123,000 |
| Animal | 4 | 10 | 9 | 82,000 |
| Total | 70 | 103 | 188 | 4,205,000 |
| Diet studies: | | | | |
| Clinical | 9 | 18 | 78 | 1,240,000 |
| Animal | 13 | 19 | 40 | 797,000 |
| Total | 22 | 37 | 118 | 2,037,000 |
| Total (drug and diet): | | | | |
| Clinical | 75 | 111 | 257 | 5,363,000 |
| Animal | 17 | 29 | 49 | 879,000 |
| Grand total | 92 | 140 | 306 | 6,242,000 |

EFFECT OF DIET ON CARDIOVASCULAR DISEASE

Mr. SMITH. Is there a program for studying the effect of diet upon cardiovascular disease that is comparable to the drug study program and, if so, what results have there been in this study?

Dr. FREDRICKSON. At the present time the Heart Institute is evaluating plans for large-scale definitive clinical trials designed to study the effect of diet upon cardiovascular disease. The program under consideration includes studies that are analogous to the current coronary drug project.

There is now considerable evidence to indicate that diet may be one of the key factors in the development of arteriosclerosis. A reasonable, and vitally important scientific hpyothesis can be constructed: appropriate regulation of dietary fat and cholesterol may affect the incidence rates of coronary heart disease—and, in particular, heart attacks. This hypothesis derives from several lines of evidence but especially from the strong association between blood cholesterol levels and the incidence of coronary heart disease, and from the repeated demonstration that blood cholesteroal levels can be significantly reduced by diet modification.

The advisability and feasibility of a definitive dietary trial has been under intensive study for some time. In 1960 the National Heart Institute supported, with grant funds, the establishment of an Executive Committee on Diet and Heart Disease under the chairmanship of Dr. Irvine H. Page. This committee explored the problems involved in mass field trials designed to determine the effect of diet modification on the prevention of coronary heart disease. The committee concluded that, on the basis of information then available, a definitive recommendation could not be formulated without undertaking certain feasibility trials. Accordingly, in 1962, the Heart Institute awarded research grants to support a national diet-heart feasibility study. This cooperative research study involved approximately 1,500 men over a 2-year study period. The study subjects included both free-living men from the general population and long-term residents in a mental institution.

In this well-designed, carefully controlled, preliminary study significant dietary modification was obtained through the use of specially prepared, fat-modified foods. The results of this study and the recommendations of these investigators have just been published as Supplement No. 1 to the March 1968 issue of Circulation. The investigators have concluded that recruitment of subjects, modification of dietary intake, and significant reduction in blood cholesterol levels are indeed feasible. Based on their study results and other scientific information, they strongly recommend that large-scale studies be undertaken to test prevention of coronary heart disease by dietary means.

The complete and detailed report of the feasibility study is now being evaluated. Even before this final report became available, the institute has established a special committee of experts to provide counsel in this area. The members of this committee are: Dr. Edward H. Ahrens, Jr., of the Rockefeller University, New York, chairman; Dr. Thomas C. Chalmers, Tufts University School of Medicine; Dr. William E. Connor, State University of Iowa; Mr. Jerome Cornfield, University of Pittsburgh School of Public Health; Dr. Seymour Dayton, Veterans' Administration Center, Los Angeles; Mr. Fred Ederer, National Heart Institute; Dr. Frederick H. Epstein, University of Michigan; Dr. Gardner McMillan, National Heart Institute; Dr. Paul Meier, University of Chicago; Dr. Seth T. Shaw, Arlington, Va.; and Dr. Eugene A. Stead, of Duke University School of Medicine.

Whether or not the Institute will recommend that a secondary dietary prevention study, that is a study comparable to the drug study program, be undertaken will depend on the recommendations of the Panel, further deliberations of the National Advisory Heart Council,

and by the Institute staff. The preliminary estimates of the Institute staff are that a well-designed, carefully controlled, clinical trial of this vitally important question will require considerable appropriation for this purpose. Depending upon the type of study chosen, up to $35 million per year could be required when it is in full operation. Apart from the findings of the diet-heart feasibility study that mass dietary studies are possible, no study on the scale of the coronary drug project has been launched.

PATENT RIGHTS ON BABB-GRIMSRUD DIALYZER

Mr. SMITH. Who has the patent rights to the Babb-Grimsrud dialyzer?

Dr. FREDRICKSON. This is really the responsibility of the National Institute of Arthritis and Metabolic Diseases, however, I have recently obtained this information from that Institute.

The Babb-Grimsrud artificial kidney has been under development for a number of years at the University of Washington, Seattle. The initial work was performed under a grant from the John A. Hartford Foundation. No patents have been applied for and any information which was developed concerning this apparatus was published in the open scientific literature (and is therefore now in the public domain and no longer exclusively patentable).

Since June 1966, continuing developmental work on this artificial kidney at the University of Washington is being funded under a contract with the National Institute of Arthritis and Metabolic Diseases. Any new developments and findings made with the aid of this contract are subject to the specific patent clauses of such PHS contracts which are given in the attached answer to the question concerning the provisions of that contract.

Mr. SMITH. What does the contract provide relative to the patent?

Dr. FREDRICKSON. The contract provides that the Assistant Secretary of the Department of Health, Education, and Welfare, has the sole and exclusive power to determine whether or not a patent application shall be filed and to determine the disposition of all rights in any invention made.

I will supply the detailed provisions of such contracts for the record.

(The information follows:)

ARTICLE V.—PROJECT OFFICER

The project officer representing the Government for the purpose of technical direction of contract performance shall be designated in writing by the Director National Institute of Arthritis and Metabolic Diseases, National Institutes of Health. The project officer is empowered to act hereunder only to the extent specified in provisions of this contract where the term "Project Officer" is used.

ARTICLE VI.—GENERAL PROVISIONS

The attached general provisions (HEW–315, August 1964 revision), forming a part of this contract, are hereby modified as follows:

*Clause 6* (equal opportunity) is deleted in its entirety and replaced by the attached "Equal Employment Opportunity" clause (HEW–386, revised October 1965).

*Clause 12* (rights in data) is deleted in its entirety and replaced by the following:

(a) The term "Subject Data" as used herein, includes writings, sound recordings, pictorial reproductions, drawings or other graphical representa-

tions, procedural manuals, forms, diagrams, work flow charts, equipment descriptions, data files and data processing or computer programs, and works of any similar nature (whether or not copyrighted), which are specified to be delivered under this contract. The term does not include financial reports, cost analyses, and other information incidental to contract administration.

(b) All subject data first produced in the performance of this contract shall be the sole property of the Government. The contractor agrees not to assert any rights at common law or equity and not to establish any claim to statutory copyright in such data. The contractor shall not publish or reproduce such data in whole or in part or in any manner or form, nor authorize others so to do, without the written consent of the Government until such time as the Government may have released such data to the public.

(c) The contractor agrees to grant and does hereby grant to the Government and to its officers, agents, and employees acting within the scope of their official duties, a royalty-free, nonexclusive, and irrevocable license thoughout the world (i) to publish, translate, reproduce, deliver, perform, use, and dispose of, in any manner, any and all data not first produced or composed in the performance of this contract but which is incorporated in the work furnished under this contract; and (ii) to authorize others so to do.

(d) The contractor shall indemnify and save and hold harmless the Government, its officers, agents and employees acting within the scope of their official duties against any liability, including costs and expenses, (i) for violation of proprietary rights, copyright or right of privacy, arising out of the publication, translation, reproduction, delivery, performance, use or disposition of any data furnished under this contract, or (ii) based upon any libelous or other unlawful matter contained in such data.

(e) Nothing contained in this clause shall imply a license to the Government under any patent or be construed as affecting the scope of any license or other right otherwise granted to the Government under any patent.

(f) Paragraphs (c) and (d) above are no applicable to material furnished to the contractor by the Government and incorporated in the work furnished under the contract; provided, such incorporated material is identified by the contractor at the time of delivery of such work.

(g) The contractor will keep NIH fully advised as to the systems and procedures employed in carrying out the contract requirements, including procedural manuals, forms, diagrams, work flow charts, equipment descriptions, data processing machine instructions (including computer programs, if prepared, and upon request provide detailed written records of such systems and procedures. In addition, one copy of principal data files and computer programs in machine processable form, if such programs are fully checked out and generally usable, shall be delivered together with sufficient written documentation to allow for independent understanding of organization, content and coding of such files and programs.

*Clause 20* (Patent Rights)—subparagraph (d) is added:

(d) In the event the contractor files a patent application on any invention described in paragraph (a) hereof, it shall include the following statement in the first paragraph of the specification and in any patent issued thereon:

The invention described herein was made in the course of, or under, a contract with the Department of Health, Education, and Welfare.

(a) As used in this clause, the term—

(1) "Invention" or "Invention or discovery" includes any art, machine, manufacture, design, or composition of matter, or any new and useful improvement thereof, or any variety of plant, which is or may be patentable under the Patent Laws of the United States of America.

(2) "Made" when used in relation to any invention or discovery means the conception or first actual or constructive reduction to practice of such invention in the course of or under the contract.

(b) Determination of Rights to Inventions made by the contractor shall be made by:

(1) the Assistant Secretary (Health and Scientific Affairs) who shall have the sole and exclusive power to determine whether or not and where a patent application shall be filed, and to determine the disposition of all

rights in such invention, including title to and rights under any patent application or patent which may issue thereon. The determination of the Assistant Secretary (Health and Scientific Affairs) on all these matters shall be accepted as final and the provisions of the clause of this contract entitled "DISPUTES" shall not apply;

(2) The Assistant Secretary (Health and Scientific Affairs) who may, upon request of the contractor, determine to exercise his option to waive rights to the invention in foreign countries.

(c) The following disclosures and reports on inventions made under the contract shall be furnished by the contractor to the contracting officer:

(1) A complete written disclosure of each such invention promptly after conception or first actual or constructive reductions to practice, whichever occurs first under this contract.

(2) Information in writing, as soon as practicable, concerning the date and identity of any public use, sale, or publication of such invention made by or known to the contractor or of any contemplated publication by the contractor.

(3) Upon request, such duly executed instruments (prepared by the Government) and such other papers as are deemed necessary to vest in the Government the rights granted it under this clause and to enable the Government to apply for and prosecute any patent application, in any country, covering each invention where the Government has the right under the clause to file such application.

(4) Interim reports on the first anniversary of the contract where extended or renewed and every year thereafter listing all inventions made during the period whether or not previously reported or certifying that no inventions were made during the applicable period.

(5) Prior to final settlement of this contract, a final report listing all such inventions including all those previously listed in interim reports, or certifying that there are no such unreported inventions.

(d) Patent agreements shall be obtained by:

(1) The contractor to effectuate the provisions of this clause from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will have no access to technical data, and except as otherwise authorized in writing by the contracting officer.

(2) The contractor who will insert in each subcontract or agreement having experimental, developmental, or research work as one of its purposes, a provision making this clause applicable to the subcontractor and its employees, except as otherwise authorized in writing by the contracting officer.

(e) Payment may be withheld under the contract either in the amount of 10 percent of the amount of this contract or $10,000, whichever is less, if the contractor fails to furnish the written disclosures for all inventions as required by (c)(1), or fails to deliver to the contracting officer the interim reports as required by (c)(4) of this clause, or fails to furnish the final report as required by (c)(5), until the contractor shall have corrected such failure(s). The withholding of any amount or subsequent payment thereof to the contractor shall not be construed as a waiver of any rights accruing to the Government under the contract. This paragraph shall not be construed as requiring the contractor to withhold any amounts from a subcontractor to enforce compliance with the patent provisions of a subcontract.

(f) In the event the contractor files a patent application on any invention made in the course of or under this contract, it shall include the following statement in the first paragraph of the specification and in any patent issued thereon:

"The invention described herein was made in the course of, or under, a contract with the Department of Health, Education, and Welfare."

JUSTIFICATION MATERIAL

Department of Health, Education, and Welfare

Public Health Service

National Heart Institute

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $167,954,000 | $169,735,000 |
| Transferred to "Office of the Surgeon General, Salaries and expenses" | -163,000 | ..... |
| Proposed transfer to "Hospitals and medical care" | -1,893,000 | ..... |
| Total | 165,898,000 | 169,735,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 64 | Research | | $105,100,000 | | $105,729,000 | | +$629,000 |
| | General research support grants | | (9,809,000) | | (9,425,000) | | (-384,000) |
| | Scientific evaluation and planning | | (163,000) | | (163,000) | | ..... |
| | Categorical clinical research centers | | (4,500,000) | | (4,500,000) | | ..... |
| | Heart cooperative drug study | | (3,820,000) | | (3,820,000) | | ..... |
| | Specialized research centers | | (800,000) | | (1,050,000) | | (+250,000) |
| 73 | Fellowships | | 7,439,000 | | 7,604,000 | | +165,000 |
| 74 | Training | | 17,696,000 | | 18,150,000 | | +454,000 |
| | Direct operations: | | | | | | |
| 76 | Laboratory and clinical research | 409 | 13,113,000 | 423 | 13,671,000 | +14 | +558,000 |
| 78 | Collaborative research and development | 42 | 17,138,000 | 42 | 19,142,000 | 0 | +2,004,000 |
| 81 | Biometry, epidemiology, and field studies | 83 | 1,747,000 | 83 | 1,765,000 | 0 | +18,000 |
| 82 | Training activities | 12 | 222,000 | 12 | 224,000 | 0 | +2,000 |
| 82 | Review and approval of grants | 105 | 2,495,000 | 110 | 2,611,000 | +5 | +116,000 |
| 83 | Program direction | 31 | 798,000 | 31 | 839,000 | 0 | +41,000 |
| | Total obligations | 682 | 165,748,000 | 701 | 169,735,000 | +19 | +3,987,000 |
| | Unobligated balance reserve | 22 | 150,000 | .. | ..... | -22 | -150,000 |
| | Total, obligations and reserve | 704 | 165,898,000 | 701 | 169,735,000 | -3 | +3,837,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 682 | 701 | +19 |
| Full time equivalent of other positions.. | 38 | 39 | +1 |
| Average number of all employees..... | 669 | 699 | +30 |
| 11 Personnel compensation: Permanent positions..... | $5,875,000 | $6,087,000 | +$212,000 |
| Positions other than permanent..... | 235,000 | 245,000 | +10,000 |
| Other personnel compensation..... | 63,000 | 63,000 | --- |
| Total personnel compensation..... | 6,173,000 | 6,395,000 | +222,000 |
| 12 Personnel benefits..... | 739,000 | 753,000 | +14,000 |
| 21 Travel and transportation of persons. | 288,000 | 300,000 | +12,000 |
| 22 Transportation of things..... | 84,000 | 90,000 | +6,000 |
| 23 Rent, communications, and utilities.. | 221,000 | 222,000 | +1,000 |
| 24 Printing and reproduction..... | 20,000 | 22,000 | +2,000 |
| 25 Other services..... | 1,340,000 | 1,583,000 | +243,000 |
| Project contracts..... | 17,180,000 | 19,180,000 | +2,000,000 |
| Payment to "National Institutes of Health management fund"..... | 7,071,000 | 7,169,000 | +98,000 |
| 26 Supplies and materials..... | 1,677,000 | 1,767,000 | +90,000 |
| 31 Equipment..... | 736,000 | 787,000 | +51,000 |
| 41 Grants, subsidies, and contributions | 130,235,000 | 131,483,000 | +1,248,000 |
| Subtotal..... | 165,764,000 | 169,751,000 | +3,987,000 |
| Deduct quarters and subsistence charges. | -16,000 | -16,000 | --- |
| Total obligations by object..... | 165,748,000 | 169,735,000 | +3,987,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $167,954,000 |
| Transferred to "Office of the Surgeon General, salaries and expenses" | -163,000 |
| Proposed transfer to "Hospitals and medical care" | -1,893,000 |
| Unobligated balance, reserve | -150,000 |
| 1968 total estimated obligations | 165,748,000 |
| 1969 estimated obligations | 169,735,000 |
| Total change | +3,987,000 |

| Increases | Base Positions | Base Amount | Change from Base Positions | Change from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. One extra day of pay in 1969 | ... | ... | ... | $20,000 |
| 2. Annualization of 1968 pay increase | ... | ... | ... | 92,000 |
| Total built-in increases | ... | ... | ... | 112,000 |
| B. Program | | | | |
| 1. Research grants | ... | $105,100,000 | ... | 629,000 |
| 2. Fellowships | ... | 7,439,000 | ... | 165,000 |
| 3. Training grants | ... | 17,696,000 | ... | 454,000 |
| 4. Laboratory and clinical research | 409 | 7,747,000 | 14 | 475,000 |
| 5. Collaborative research and development | 42 | 17,064,000 | ... | 2,000,000 |
| 6. Review and approval of grants | 105 | 1,271,000 | 5 | 35,000 |
| 7. Program direction | 31 | 543,000 | ... | 19,000 |
| Total program increases | ... | ..... | 19 | 3,777,000 |
| C. Payment to "National Institutes of Health management fund" for centrally-furnished services: | | | | |
| Laboratory and clinical research | ... | 5,366,000 | ... | 18,000 |
| Collaborative research and development | ... | 74,000 | ... | -2,000 |
| Biometry, epidemiology, and field studies | ... | 127,000 | ... | 2,000 |
| Direct training | ... | 25,000 | ... | ..... |
| Review & approval of grants | ... | 1,224,000 | ... | 63,000 |
| Program direction | ... | 255,000 | ... | 17,000 |
| Total management fund | ... | ..... | ... | 98,000 |
| Total net changes requested | | | | +3,987,000 |

Explanation of Changes

Research grants--The net increase of $629,000 will provide $263,000 for the noncompeting continuation of existing regular research grants, $500,000 for the competing continuation of existing regular program project grants, and $250,000 for specialized cardiovascular research and training centers. These increases are partially offset by a decrease of $384,000 for general research support grants.

Fellowships--The increase of $165,000 will provide for stipend increases.

Training grants--The increase of $454,000 will provide for additional stipend allowances in the graduate cardiovascular training area.

Laboratory and clinical research--The program increase of $475,000 and 19 positions will allow for the continuation and normal expansion of ongoing programs and for accelerated expansion in the study of biochemical aspects of disease from the cellular level.

Collaborative research and development--The program increase of $2,000,000 will be used to further research and development in the artificial heart myocardial infarction program.

Review and approval of grants-- The program increase of $35,000 and 5 positions is for analytical and reporting functions.

Program direction--The program increase of $19,000 is needed for program planning within the Institute and for ad hoc review groups.

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301--Research and Investigation, in General | Indefinite |
| Title IV, Part B--National Heart Institute | Indefinite |

PUBLIC HEALTH SERVICE ACT

Title IV--National Research Institutes, Part B, National Heart Institute

Section 411. There is hereby established in the Public Health Service a National Heart Institute (hereafter in this part referred to as the "Institute").

Section 412. In carrying out the purposes of section 301 with respect to heart diseases the Surgeon General, through the Institute and in cooperation with the National Advisory Heart Council (hereafter in this part referred to as the "Council"), shall--

(a) conduct, assist, and foster researches, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of heart diseases;

(d) make grants-in-aid to universities, hospitals, laboratories, and other public or private agencies and institutions, and to individuals for such research projects relating to heart diseases as are recommended by the Council, including grants to such agencies and institutions for the Council, including grants to such agencies and institutions for the construction, acquisition, leasing, equipment, and maintenance of such hospital, clinic, laboratory, and related facilities, and for the care of such patients therein, as are necessary for such research;

(g) in accordance with regulations and from funds appropriated or donated for the purpose (1) establish and maintain research fellowships in the Institute and elsewhere with such stipends and allowances (including travel and subsistence expenses) as he may deem necessary to train research workers and procure the assistance of the most brilliant and promising research fellows from the United States and abroad, and, in addition, provide for such fellowships through grants, upon recommendation of the Council, to public and other nonprofit institutions; and (2) provide training and instruction and establish and maintain traineeships, in the Institute and elsewhere in matters relating to the diagnosis, prevention, and treatment of heart diseases with such stipends and allowances (including travel and subsistence expenses) for trainees as he may deem necessary, the number of persons receiving such training and instruction, and the number of persons holding such traineeships, to be fixed by the Council and, in addition, provide for such training, instruction, and traineeships through grants, upon recommendation of the Council, to public and other nonprofit institutions.

Explanation of Transfers

| | 1968 Estimate | 1969 Estimate | Purpose |
|---|---|---|---|
| Transfer to: | | | |
| "Office of the Surgeon General, salaries and expenses"..... | - $163,000 | ..... | For centralized services concerned with grants policy and procedure functions; and for buildings and facilities services. |
| Proposed transfer to: | | | |
| "Hospitals and medical care"... | -1,893,000 | ..... | To provide for increased pay costs in 1968. |

Justification

National Heart Institute

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 682 | $6,912,000 | 701 | $7,148,000 | +19 | +$236,000 |
| Other expenses..... | ... | 158,836,000 | ... | 162,587,000 | .... | +3,751,000 |
| Total..... | 682 | 165,748,000 | 701 | 169,735,000 | +19 | +3,987,000 |

General Statement

In its search for the cure, alleviation, and prevention of cardiovascular diseases, the National Heart Institute conducts and supports research programs of great scope and diversity. Its research projects range from epidemiological studies on large population groups to studies on individual cells and cellular components and on the biochemical reactions occurring within them.

The diversity of this research is dictated by the complexity of the problems posed by the cardiovascular diseases. For the most part, their causes are not known with certainty; but in many instances, a constellation of complex factors--genetic, environmental, and physiological--may operate in their development and in their protean clinical manifestations. For example, atherosclerosis appears to be related not only to metabolic imbalance, but also to blood-clotting mechanisms and the dynamics of flow in vessels; and susceptibiliity to the disease may be influenced by such factors as age, sex, diet, physical activity, and psychic stress. Congenital heart disease may arise from genetic factors or from a variety of noxious prenatal factors affecting the fetus at critical stages of its development.

For reasons such as these, it has been both necessary and desirable to deploy our research manpower and resources along a wide variety of research approaches.

However, the broad base of fundamental and clinical knowledge accumulated through these research programs has also made it possible to mount a number of programs of research and development aimed directly at the solution of specific health problems posed by the cardiovascular diseases. The development of heart-assist devices to provide temporary or permanent support to a failing circulation; the clinical evaluation of lipid-lowering drugs to reduce recurrent heart attacks and to prolong the lives of heart attack victims; the development of instrumentation and automated techniques for the mass production of blood components for a wide variety of clinical uses--all of these are goals of special research and development programs already under way. And all, if successful, should have profound and far-reaching effects on the health and welfare of our people.

Research Projects

There follows a brief description of grant-supported research in each of the major cardiovascular-disease categories. Plans for 1968 and 1969 are primarily a continuation of current research in these areas, as indicated in the research grants program analysis table at the end of the research grant justification.

Atherosclerosis is, by far, the most prevalent of all cardiovascular disorders. If it could be entirely eliminated in the American population, or even if only some of its complications (such as heart attacks, strokes, and congestive heart failure) could be prevented, hundreds of thousands of lives might be spared or prolonged.

During the past decade, there has been nearly a tenfold increase in the number of research projects in this field; and currently, in terms of research funds expended, atherosclerosis is the largest single disease category in the Heart Institute program.

A large segment of this research deals with mechanisms whereby fats are absorbed, transported, synthesized, and broken down within the body. Derangements in one or more of these processes are thought to underlie the elevated blood levels of cholesterol and other fats that predispose to atherosclerosis. Other important research is concerned with the effects of diet on blood-lipid levels and the evaluation of lipid-lowering diets and drugs as potential means of preventing atherosclerosis, retarding its development, or perhaps reversing the course of the disease.

Another large segment of atherosclerosis research is concerned with the body's clotting and clot-dissolving mechanisms, because clotting complications account for most heart attacks, strokes, and other lethal or crippling manifestations of the disease. This research includes basic studies on coagulation mechanisms; on elevated blood lipids and other factors that may predispose the victim of atherosclerosis to clotting complications; and on anticoagulant and clot-dissolving agents that may provide effective therapeutic measures against heart attacks, strokes, and other thromboembolic complications of atherosclerosis.

The remainder of the research in this field involves many different disciplines and lines of attack. They vary from studies on the influence of different diets on the atherosclerotic lesion in expeimental animals to the development of new instruments for measuring arterial blood flow, and the study of the personality characteristics and "risk factors" in patients who have been victims of one or another complication of the disease.

Hypertension is one of the most commonly encountered forms of cardiovascular disease. An estimated 17,000,000 Americans between the ages of 18 and 79 have high blood pressure, and about 10,500,000 have heart disease as a consequence of hypertension. Hypertension accelerates the development of atherosclerosis and is a major cause of strokes, heart failure, and kidney failure.

As much as 15 percent of all cases of hypertension are secondary to kidney disease or other pathologic processes that are potentially curable if promptly diagnosed and corrected. Improved techniques for the diagnosis of disorders

that can cause secondary hypertension for selecting patients who may benefit from surgery are thus important goals.

Most victims of hypertension, however, suffer from "primary" or "essential" hypertension, a disease of unknown origin. Ignorance of the cause of essential hypertension has not, however, prevented the development of a steadily growing number of effective drugs for reducing blood pressure in hypertensive patients. Although they do not cure the disease, a variety of drugs have been developed for controlling hypertension of all degrees of severity. The resulting decline in mortality has been striking; but none of these drugs is perfect, and some have unpleasant and sometimes serious side effects. Thus the quest for new or improved therapeutic agents continues.

Other important areas of study include research on fluid and electrolyte metabolism; the possible role of endocrine disturbances in hypertension; hereditary or environmental factors affecting the development or causes of the disease; and nerve and hormone mechanisms involved in blood-pressure control.

NHI also supports research concerned with kidney transplants and artificial kidneys for the management of kidney failure, a common complication of hypertension. These efforts are effectively supplemented by similar activities of NIAMD.

Cerebrovascular diseases account for about 200,000 deaths a year--a toll exceeded only by heart disease and cancer. There are no reliable statistics on the number of persons partially or completely disabled by cerebrovascular disease, but it may exceed a million. Although mortality is concentrated in older people, the mid-life toll is also high: in 1965 some 39,600 cerebrovascular deaths occurred in Americans aged 25 to 64.

The NHI Framingham Study has demonstrated that the most common cause of stroke is blood clots forming in the arteries supplying the brain. Initial mortality from acute cerebral thrombosis was approximately 15 percent in this series, and fully half of the survivors were left with permanent disability. Mortality from cerebral hemorrhage, another common cause of stroke, is considerably higher than this.

A stroke is usually the consequence of other circulatory diseases. Hypertension, for example, both predisposes patients to a stroke and aggravates its clinical effects. Atherosclerosis can weaken affected blood vessels supplying the brain, predispose them to rupture, and create conditions favorable to the formation of blood clots.

Within recent years there have been many significant advances in the clinical attack on the stroke problem: objective techniques for measurement of blood flow to the brain have been developed; new x-ray techniques provide safe and effective means of detecting obstructive disease affecting the brain's major "feedlines" in the chest and neck, an important and potentially curable cause of cerebral insufficiency. There has been a sharper definition, and hence a basis for more appropriate therapy, of a variety of stroke syndromes.

Over half of NHI research grants concerned with stroke involve perfecting reconstructive techniques in vascular surgery and developing better anesthetic agents and methods. Most of the remainder are concerned with improved methods of diagnosis and medical management of cerebrovascular disease.

The Heart Institute works closely with the National Institute of Neurological Diseases and Blindness in the assessment and development of relevant scientific programs and resources. The research programs of the two Institutes are often complementary: for example, NINDB is supporting a cooperative study of strokes due to brain hemorrhage, while the Heart Institute is conducting a similar study of strokes associated with diseased neck vessels supplying the brain.

To date, the preponderant effort has been in the treatment and palliation of the cerebrovascular diseases. However, other research, concerned with prevention, is attempting to define factors in the person or his environment that increase susceptibility to stroke and seeking improved methods of diagnosis, so that stroke-prone individuals can be identified early and measures initiated that may avert or postpone the onset of crippling or lethal consequences of cerebrovascular disease.

Congenital heart disease caused the deaths of more than 7,300 infants under two years of age during 1964. One-third of all congenital-heart-disease patients die in the first month, and most of these in the first week of life. Although surgical treatment has continued to improve, it is still extremely risky in infants less than six months of age.

The NHI research program places primary emphasis on the improvement of methods for the diagnosis and evaluation of congenital heart defects and on the perfection of surgical methods for correcting them. As a result of this research, most of the commoner types of congenital heart disease, and many of the rarer forms, can be completely corrected or else palliated by surgery.

The NHI program is complemented by the programs of two other Institutes. The Neurological Institute has a large organized program of perinatal research to define the prevalence and to seek the causes of various types of congenital disorders. Then, the National Institute of Child Health and Human Development supports research in embryology and teratology, the experimental production of congenital anomalies.

Rheumatic fever and rheumatic heart disease have declined steadily as causes of death and disability during the past several decades, but both continue to occur in significant numbers of our people to constitute an important health problem.

The evidence associating rheumatic fever with a preceding streptococcal infection is overwhelming, but the underlying mechanisms are largely obscure. Research results are most consistent with an inappropriate immunologic reaction triggered in the patient by the products of certain hemolytic streptococci. The fact that rheumatic fever develops in less than 1 percent of people who become infected with these streptococci suggests that some factor or factors in the affected person himself are important in the development of the disease. Until highly susceptible individuals can be identified in advance and

effectively protected by antibiotics or other means, rheumatic fever and rheumatic heart disease will continue to occur.

A consistently reliable laboratory test for the diagnosis of cardiac involvement in rheumatic-fever victims is badly needed, as are effective techniques for preventing or reducing the severity of damage when the heart is attacked by the disease. More research is also needed on the natural and post-therapeutic history of these disorders, not merely for decisions about the relative value of various valve replacements (artificial valves or valve transplants) and surgical procedures, but also for the crucial decisions in determining the best time for surgery and the type of patient most likely to benefit.

Mortality from cardiopulmonary diseases, chiefly chronic bronchitis and emphysema, increased more than fourfold between 1953 and 1963. Moreover, the estimates of prevalence are alarming: not less than 10 percent of middle-aged and elderly Americans are afflicted. As a disabling disease, emphysema is second only to heart disease, disability allowances now exceed $80,000,000 each year.

The exact causes of emphysema are largely unknown, but a number of factors, such as cigaret smoking, air pollution, allergy, and respiratory infections, are strongly suspected of playing important roles in its development. While recognition of these factors has led to reasonable programs to prevent severe disability, and while they may indicate promising research leads, we do not yet understand either the causes of emphysema or its mode of development. For example, we do not know whether it is primarily a degenerative process resulting from interference with the circulation in the lungs; a consequence of chronic infection--e.g., chronic bronchitis--or of repeated intermittent infection.

The complexities posed by these diseases require a diversity of research approaches.. The Heart Institute currently supports a large body of research concerned with lung structure and lung function; the nerve, hormonal, chemical, and mechanical factors affecting respiration; gas transport and gas exchange; the destruction, repair, and regeneration of lung tissues; and the causes, clinical physiology, diagnosis and treatment of pulmonary disease.

This research has led to the development of a wide variety of pulmonary function tests that aid in the early detection of pulmonary disease and in the evaluation of therapeutic measures. Of great potential importance in the early detection of emphysema is the recent development of procedures employing rapid single-breath tests of lung function that are applicable to the mass screening of large populations.

Basic studies in respiratory physiology, by helping to clarify the role of the central nervous system, chemoreceptors, and other factors on respiratory drive, may provide clues to the development of improved drugs and other therapeutic measures to relieve the breathlessness of emphysema. Other studies, centering on the various secretions of the lung, might lead to the development of more effective mucolyte agents and expectorants for clearing clogged airway passages.

Studies on the destruction, repair, and regeneration of lung tissue may provide information on how emphysema does its damage and may provide clues to effective measures for retarding or halting the course of the disease.

Other grants support studies directed toward devising improved mechanical oxygenators for use in cardiac and pulmonary surgery; new machines and techniques for long-term respiratory assistance in patients with acute or chronic respiratory failure; and means of avoiding respiratory failure in conjunction with anesthesia for surgical operations.

The National Institute of Allergy and Infectious Diseases is also concerned with emphysema, particularly in the role of allergic reactions, repeated acute respiratory infections, and chronic infections that may underlie the development of the disease or adversely affect its clinical cause.

Heart failure is generally classified into acute and chronic forms. The acute form includes shock, some types of fainting, and some forms of sudden death--often due to profound disturbances of heart rhythm. The chronic form of circulatory failure is generally known as congestive heart failure and denotes prolonged impairment of the ability of the heart to maintain an adequate blood flow to the tissue.

Most of the research support in this disease category is for studies on the underlying causes of heart failure. The answer may be found in intensive studies on the ultrastructure and arrangement of the heart muscle fibers and contractile proteins--or it may lie somewhere in the complex biochemical mechanisms by which the heart generates chemical energy and harnesses that energy to drive the contractile process--or both.

Another important segment of research deals with the treatment of congestive heart failure. The time-honored drug, digitalis, has been supplemented by a number of additional powerful cardiac stimulants and blood-vessel constrictors that provide much-needed support to a failing circulation. A variety of powerful diuretic agents is available to combat the excessive fluid retention (edema) that often accompanies congestive failure, especially the pulmonary edema that can pose a serious threat to the patient's life. The development of effective drugs for the prevention or suppression of heart arrhythmias and electrical means of treating cardiac arrest (heart standstill) constitute other research advances of great clinical importance.

A large body of research is concerned with the basic physiology of the heart and blood vessels, particularly mechanisms regulating normal heart performance, biochemical and mechanical factors affecting contractility, and the interplay of these factors in health and during the development of heart failure.

Recent dramatic events in heart transplantation have underscored the need for additional knowledge if this apparently promising approach to heart failure is to become clinically feasible. Two major obstacles to progress in this field are 1) rejection of the transplant by the immunological mechanisms of the recipient and 2) the lack of suitable means for organ preservation.

The current level of NHI research support in organ transplantation is about $5,000,000. Of this, over $1,300,000 is for support of 64 projects directly concerned with heart transplantation; the remainder is concerned with problems of kidney, lung, and liver transplants and with immunological studies basic to organ transplantation in general. This program will be strengthened and expanded as available funds permit.

Summaries of some of the results of research support in 1967 pertaining to these research areas appear in the research highlights that accompany the statement of the Director, National Heart Institute. The 1969 budget request for regular research grant programs includes an increase of $763,000. Of this, $263,000 is requested for noncompeting continuation requirements and $500,000 for competing projects.

Special Programs

General Research Support Grants: The decrease of $384,000 represents the Institute's proportionate share of the proposed budget for this program.

Categorical Clinical Research Centers: The same level of support, $4,500,000, is continued from 1968 to 1969 for the research resources of in-depth, multidisciplinary investigations in many of the research areas outlined in the presentation above for regular research grant programs.

Cooperative Study of Drugs and Coronary Heart Disease: This program has as its primary objective the determination of whether certain drugs that reduce the concentration of blood lipids, or fats, are capable of improving survival among patients with coronary heart disease. The second objective is to determine whether the degree to which these drugs lower serum lipids is correlated with their effect on mortality and heart-attack rates. By studying just as intensively the individuals in the study who do not receive lipid-lowering agents, the investigators will obtain valuable further information concerning the outlook for men who have survived an initial myocardial infarction. Finally, the study aims at accumulating additional knowledge and experience in the technology of cooperative clinical trials in cardiovascular disease.

In human terms, if the effectiveness of these drugs is in fact related to their ability to lower blood fats, it can be calculated that such drugs might be able to reduce the number of recurrent heart attacks by 30 percent. This would have obvious and important consequences for the three million or more Americans with definite coronary heart disease and the additional two million suspected of having it. Furthermore, demonstration of the principle that drugs which lower blood lipids can improve survival would stimulate the development of still more satisfactory lipid-lowering drugs for the treatment and prevention of coronary heart disease.

During the summer and fall of 1965 protocols for this far-reaching study were perfected, operational details were refined, and the Congress provided funds in 1966 and 1967 to fill out the total of 55 clinics anticipated in the study plans. During 1968 and 1969 that plan calls for these clinics to recruit approximately 8,400 patients to be followed for a 5-year period. Additional material pertaining to this study is contained in the Progress Report on Programmed Activities which accompanies the statement of the Director, National Heart Institute.

Specialized Cardiovascular Research and Training Centers: The Heart Institute is undertaking to establish and support a limited number of such highly selected centers of excellence in which large and stable investments are deliberately made in groups of investigators capable of imaginative and creative research.

Each center will be an organizational unit, established within a university or similar institution, for carrying out research and training related to a broad range of cardiovascular disease problems. Ideally, it will be organized under a single outstanding director and staffed by a core group of scientists representing not only the various clinical disciplines but also the physical, engineering, and social sciences, each contributing his special expertise where needed in the solution of complex problems. The members of the core group would work in sufficiently close proximity to facilitate the free exchange of information, ideas, and constructive criticism. This, in turn, would facilitate the early identification and follow-up of promising new leads or more concerted research attacks on particularly difficult or troublesome problems.

Although all centers will carry out research programs of considerable breadth and depth, NHI recognizes that areas of special emphasis will vary from institution to institution. However, NHI feels that all centers should be heavily involved in research relevant to the solution of clinical problems posed by the cardiovascular diseases. All should carry out vigorous training programs designed to attract high quality trainees in a variety of disciplines and to arm them with the finest research and clinical skills that modern science can provide.

The Heart Institute believes that the center concept will permit simplification and provide greater efficiency in the administration and use of grant funds. Specialized equipment, facilities, and other resources can be provided with greater economy. Moreover, the sustained high level of productivity and excellence expected of each center will justify support of greater stability and continuity.

The center grant will allow for inclusion of funds for research inpatient and outpatient care, for alteration and renovation of space as dictated by the needs of the program, for salaries of all categories of personnel, and for the purchase of equipment and supplies. Funds for construction will be a prerequisite for establishment of most centers. These will be obtained through the NIH Division ofResearch Facilities and Resources on a matching funds basis.

The request for such funds will be reviewed concomitantly with the request for operational support from the Heart Institute.

In time, given continued availability of planning grant funds, enough institutions should develop the capabilities needed to qualify for center status so that a broad geographical distribution can be achieved. But excellence must be the primary consideration, for NHI hopes that the centers to be established will have a profound and beneficial effect on medical research and patient care, not only in the regions where they are located, but throughout this country and the world.

From 1966-1968 the Heart Institute has budgeted $800,000 each year for the planning of such centers. This amount is increased to $1,050,000 in 1969. The National Heart Institute proposes to develop up to twelve of these centers by 1973.

Research Grants Program Analysis

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Atherosclerosis | $16,858,000 | $17,007,000 | +$149,000 |
| Hypertension | 13,073,000 | 13,189,000 | +116,000 |
| Cerebrovascular disease | 1,978,000 | 1,996,000 | +18,000 |
| Congenital heart disease | 6,881,000 | 6,942,000 | +61,000 |
| Rheumatic fever and heart disease | 2,924,000 | 2,950,000 | +26,000 |
| Cardiopulmonary disease | 6,193,000 | 6,248,000 | +55,000 |
| Heart failure and shock | 15,997,000 | 16,139,000 | +142,000 |
| Coronary artery disease | 6,279,000 | 6,334,000 | +55,000 |
| Thromboembolic and hemorrhagic dis... | 8,687,000 | 8,764,000 | +77,000 |
| Other cardiovascular diseases | 7,138,000 | 7,202,000 | +64,000 |
| Subtotal | 86,008,000 | 86,771,000 | +763,000 |
| General research support grants | 9,809,000 | 9,425,000 | -384,000 |
| Scientific evaluation | 163,000 | 163,000 | --- |
| Categorical clinical research centers | 4,500,000 | 4,500,000 | --- |
| Heart cooperative drug study | 3,820,000 | 3,820,000 | --- |
| Specialized research centers | 800,000 | 1,050,000 | +250,000 |
| Total research grants | 105,100,000 | 105,729,000 | +629,000 |

Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Noncompeting continuations | 1,425 | $60,855,000 | 1,248 | $61,118,000 | -177 | +$263,000 |
| Competing projects | 475 | 21,353,000 | 420 | 21,853,000 | -55 | +500,000 |
| Supplementals | (250) | 3,800,000 | (250) | 3,800,000 | -- | --- |
| Subtotal, regular program | 1,900 | 86,008,000 | 1,668 | 86,771,000 | -232 | +763,000 |
| General research support grants | | 9,809,000 | | 9,425,000 | | -384,000 |
| Scientific evaluation and planning | | 163,000 | | 163,000 | | --- |
| Categorical clinical research centers | | 4,500,000 | | 4,500,000 | | --- |
| Heart cooperative drug study | | 3,820,000 | | 3,820,000 | | --- |
| Specialized research centers | | 800,000 | | 1,050,000 | | +250,000 |
| Total, research grants | | 105,100,000 | | 105,729,000 | | +629,000 |

## Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total fellowships..... | $7,439,000 | $7,604,000 | +$165,000 |

### Introduction

The primary objective of the fellowship programs is to increase the number of scientists qualified to carry on independent cardiovascular research.

### Program plans in 1968 and 1969

The above objective is carried out through four means: (1) the postdoctoral program encourages young physicians to obtain research training and experience that will enable them to utilize their medical knowledge more effectively in research on cardiovascular disease; (2) the special research fellowship for the more advanced scientist to be exposed to improved methods and to attain new skills by means of unusual training experience in research laboratories other than his own; (3) the research career development award program supports the younger investigator of demonstrated ability; (4) the research career award program will continue to provide stable support for the senior investigator.

The $165,000 increase will allow for increments to stipend awards.

### Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Continuations: | | | | | | |
| Noncompeting..... | 252 | $4,954,000 | 249 | $5,271,000 | -3 | +$317,000 |
| Competing..... | 35 | 719,000 | 42 | 819,000 | +7 | +100,000 |
| Supplementals..... | (20) | 35,000 | (20) | 35,000 | 0 | 0 |
| New..... | 141 | 1,731,000 | 122 | 1,479,000 | -19 | -252,000 |
| Total, fellowships. | 428 | 7,439,000 | 413 | 7,604,000 | -15 | +165,000 |

### Fellowships (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Postdoctoral..... | 120 | $1,090,000 | 102 | $926,000 | -8 | -$164,000 |
| Special..... | 97 | 1,096,000 | 97 | 1,164,000 | 0 | +68,000 |
| Research Career: | | | | | | |
| Career..... | 35 | 1,014,000 | 33 | 1,000,000 | -2 | -14,000 |
| Development awards.. | 176 | 4,239,000 | 181 | 4,514,000 | -5 | +275,000 |
| Total, fellowships. | 428 | 7,439,000 | 413 | 7,604,000 | -15 | +165,000 |

## Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants..... | $17,696,000 | $18,150,000 | +$454,000 |

### Introduction

The training grant programs of the National Heart Institute are designed to: (1) attract individuals to a career in the cardiovascular field; and (2) to provide the best possible training for potential cardiovascular investigators, cardiologists, nephrologists, pulmonologists, and cardiovascular surgeons and radiologists. In order to achieve these goals, the Institute makes available undergraduate training grants, graduate training grants, and graduate clinical training grants.

### Undergraduate Training Grants

Undergraduate training grants are currently made to a total of 110 schools of medicine, schools of osteopathy, and schools of public health. These grants are utilized to strengthen the cardiovascular-teaching potential at the undergraduate level. By strengthening cardiovascular teaching and by introducing students at an early stage to the cardiovascular field, a higher percentage of top students are provided with the foundation for a cardiovascular career.

### Graduate Training Grants

Graduate training grants are available to institutions that can provide excellent training for individuals already holding the Ph.D., M.D., D.O., or D.V.M. degree. The graduate research training grants are designed to produce investigators who will subsequently contribute significantly to the mission of the National Heart Institute. The graduate clinical training grants are utilized to prepare physicians as cardiologists, nephrologists, pulmonologists, cardiovascular surgeons and radiologists. Such training differs from an advanced residency in that the trainee is placed in a graduate environment which not only advances his knowledge and techniques but also introduces him to research. Thus he becomes not only a skilled clinician but a specialist who will be able to evaluate research data critically, to translate the results of research for patient care, and to keep abreast of his field.

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Continuations: | | | | | | |
| Noncompeting..... | 347 | $15,849,000 | 320 | $15,338,000 | -27 | -$511,000 |
| Competing..... | 24 | 1,000,000 | 40 | 2,200,000 | +16 | +1,200,000 |
| Supplementals..... | (14) | 200,000 | (14) | 200,000 | (0) | 0 |
| New..... | 14 | 647,000 | 8 | 412,000 | -6 | -235,000 |
| Total, training grants..... | 385 | 17,696,000 | 368 | 18,150,000 | -17 | +454,000 |

Training Grants (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Undergraduate..... | 110 | $2,670,000 | 111 | $2,685,000 | +1 | +$15,000 |
| Graduate..... | 275 | 15,026,000 | 257 | 15,465,000 | -18 | +439,000 |
| Total, training grants..... | 385 | 17,696,000 | 368 | 18,150,000 | -17 | +454,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefit | 409 | $4,215,000 | 423 | $4,373,000 | +14 | +$158,000 |
| Other expenses | | 8,898,000 | | 9,298,000 | | +400,000 |
| Total | 409 | 13,113,000 | 423 | 13,671,000 | +14 | +558,000 |

The Institute's laboratory and clinical research program has provided an effective blend of fundamental studies of the cardiovascular system, with research aimed directly at the solution of specific clinical problems posed by the cardiovascular diseases. A staff of approximately 170 professional scientists, with about an equal number of supporting staff, is devoted to this research program.

Six laboratories and branches of the National Heart Institute are involved in a vigorous program of clinical research--usually conducted concurrently with laboratory research efforts. At present 100 research beds in the NIH Clinical Center are allocated to these Heart Institute studies; in addition, research subjects are studied on an out-patient basis.

The fundamental research effort of the intramural program has received deliberate emphasis. Most cardiovascular diseases have their roots in subtle and complex metabolic processes and in the mechanisms that control or regulate these processes. A fuller exploration of these processes will improve our basic understanding of these disorders and will, thereby, provide improved methods of diagnosis, treatment, and prevention.

The close association between basic and clinical research activities within the intramural program has been highly advantageous. It provides for the more rapid clinical testing and application of those findings from basic studies that show promise in the solution of clinical problems.

In terms of budget and scientific staff, the intramural research program is modest indeed, yet the findings of Heart Institute scientists have exerted profound effects in practically every major area of cardiovascular research.

Its scientists pioneered in the use of enzyme inhibitors in the treatment of hypertension, discovered and proved the therapeutic potential of several antihypertensive drugs now in wide clinical use, and have made major contributions to scientific knowledge concerning the mechanisms by which many such agents lower blood pressure.

They have also made substantial contributions to our understanding of nerve and hormonal factors that regulate heart performance, mechanical and biochemical determinants of heart-muscle contractility, and the mechanisms by which the autonomic nervous system and various cardiac stimulants provide support to a failing circulation.

They have developed important new techniques for the detection and clinical evaluation of various types of congenital and acquired heart disease and have compiled an enviable record of success in the surgical treatment of these disorders.

Their work has helped to define more fully many of the complex processes involved in the synthesis, transport, and metabolism of cholesterol and other fats, and to identify and classify certain heritable disorders of fat storage and metabolism that are frequently associated with elevated blood-lipid levels and accelerated development of atherosclerosis.

These are only a few of the major accomplishments stemming from the work of this relatively small group of scientists.

The 1969 program increase of $475,000 allows for: (1) $175,000 for the outfitting of newly assigned laboratory space. This space will relieve crowded laboratory conditions and permit expansion of present programs that offer promise. (2) $150,000 is also requested for increases in selected other objects of research costs, such as data computation, purchase of equipment, and laboratory supplies. (3) Additional positions and funds are requested for expansion of the study of biochemical aspects of disease from the cellular level. Seven positions and $75,000 are requested to provide a much needed expansion for the Section on Polypeptide Hormones in the Laboratory of Molecular Diseases, which is making major contributions to the understanding of the structure, function, and immunologic assay of polypeptide hormones important in calcium and bone metabolism. Seven positions and $75,000 are also requested for the Section on Enzymes and Metabolism, Laboratory of Clinical Biochemistry, which is concerned with the intermediary metabolism of enzymes involved in amino acid metabolism and with the role of the various co-enzymes related to these reactions.

Included in the increase is $65,000 for mandatory items such as annualization of the 1968 pay increase and the one extra day of pay in 1969. There are also increases of $18,000 for centrally furnished services from the "National Institutes of Health management fund."

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits.. | 42 | $337,000 | 42 | $343,000 | -- | +$6,000 |
| Other expenses..... | | 16,801,000 | | 18,799,000 | | +1,998,000 |
| Total..... | 42 | 17,138,000 | 42 | 19,142,000 | -- | +2,004,000 |

Introduction

This activity includes (1) the Artificial Heart-Myocardial Infarction Program, (2) the direct support of the Heart Cooperative Drug Study, and (3) the National Blood Resource Program.

Artificial Heart-Myocardial Infarction Program

This program has as its primary goals (1) the development of devices and techniques for assisting a failing circulation and (2) reduction of death and disability from acute heart attacks. The program is combining biomedical and bioengineering approaches to this enormous health problem.

The Artificial Heart Branch is presently concentrating on the development and refinement of devices and techniques for providing pumping assistance to damaged or failing hearts. Later, with the closure of some formidable gaps presently existing in key areas of physiology and bioengineering, it is anticipated that the program will drive for the more ambitious goals of permanent assist devices and, possibly, a total replacement for hearts damaged beyond salvage.

Since June of 1964, when this program got underway, the Artificial Heart Branch has let 73 contracts totalling approximately $12,000,000 to chemical companies, electronic and engineering firms, other elements of private industry, and academic institutions. These contracts have supported research to identify and attack specific physiological, biochemical, engineering, and related problems in this field. Although the emphasis is on heart-assist devices, most areas of research--materials, pump designs, power sources, control mechanisms, and physiological problems of assisted circulation--are also fundamental to the development of permanent assist devices and artificial hearts.

The quest for blood-compatible materials has been a major concern since the inception of the program. Although the ideal material has not yet been developed, four or five appear promising: they do not cause clotting when exposed to blood for prolonged periods. Further development and improvement of these materials will be undertaken to increase their suitability for the construction of heart-assist devices.

Several new assist devices are nearing the developmental stage where they can be clinically tested and five others have already had limited clinical trials. These devices, used with modest success, have included veno-arterial pumping with oxygenation, the DeBakey partial bypass device, the Kantrowitz mechanical auxiliary ventricle, intra-aortic balloons, and counter pulsation.

The Medical Branch of the Artificial Heart-Myocardial Infarction Program is supporting the establishment of Myocardial Infarction Research Units at 5 university medical centers and hospitals. Eventually, 6-12 will be established. These Units will be specially equipped and staffed to conduct intensive research on acute heart attacks and their complications while providing the finest medical care to the heart-attack patients. The goal is the acquisition of new knowledge needed for improving all phases of medical care for heart-attack cases. Some specific research goals:

- To learn as much as possible about the presently unpredictable clinical course of the acute heart attacks.
- To determine what drugs or other measures might be used to minimize the injury suffered by the heart muscle.
- To identify and define factors that operate in the development of potentially lethal complications of the attack. These include abnormalities of heart rhythm that may progress swiftly to cardiac standstill and the complete collapse of the circulation that may occur with cardiogenic shock.
- To provide more rational bases for all phases of diagnosis, treatment, and patient care.
- To evaluate more precisely and thoroughly than has previously been possible both accepted methods of treatment and promising new ones, including mechanical devices and techniques to provide pumping assistance to damaged or failing hearts.

The Units established thus far have already begun to conduct research and to collaborate on key issues of scientific planning and evaluation. Clinical studies in the units are being supplemented with extensive research in laboratory animals.

The program has also completed negotiations for 5 contracts aimed at developing a reliable and reproducible model of myocardial infarction in animals. Such a model, we believe, will be immensely valuable in future research in this problem.

The program increase of $2,000,000 in 1969 will be used in the artificial heart program for additional basic research, evaluation and development of materials, blood pump and oxygenator components of circulatory assist devices, and energy sub-systems; for more rapid and effective development of total system's testing and evaluation; and for increased myocardial infarction studies.

## The National Blood Resource Program

Major goals of this program are (1) to survey our Nation's blood resources and their utilization in terms of present and foreseeable needs; and (2) to meet a steadily accelerating demand for blood fractions without undue strains on these resources through improvements in technology that will make possible the more efficient production, storage, and distribution of blood products.

Some specific goals of the program are

- To devise efficient, highly automated methods for the mass production of plasma and cellular fractions of blood (red cells, white cells, platelets).
- To develop improved, high-yield techniques for the large-scale fractionation of plasma to provide albumin, gamma globulin, blood clotting factors, and other medically important protein fractions.
- To investigate additives for prolonging the shelf life of whole blood and cellular fractions stored under standard conditions and improve techniques for preservation by freezing.
- To study the feasibility of a computerized national or regional daily shelf inventory system for blood and blood products.

During the past year, the program awarded a large contract to the American National Red Cross for developmental work in blood fractionation. This work will be continued during 1968.

Another major project, initiated last year and to be completed in fiscal year 1968, is a series of studies to verify the effectiveness of adenine as a blood preservative, to ascertain its effects on blood components, and to establish the safety of adenine-treated blood and blood products for clinical use. Preliminary evidence indicates that adenine may significantly prolong, perhaps double the time that blood can be stored without deterioration (presently only 21 days). If this compound performs up to expectations, it should substantially reduce presently unavoidable losses of whole blood through outdating in storage.

Scheduled to get underway this year is a cooperative clinical trial of the clot-dissolving agents urokinase and streptokinase against blood clots in the pulmonary circulation. Such drugs hold great promise in combatting clotting complications of blood-vessel disease, but the clinical value has not yet been convincingly demonstrated in carefully controlled trials. These studies will be an essential prelude to possible future trials of clot-dissolving drugs against coronary occlusion and certain strokes.

Another major project will be a study of the feasibility of a computer-based national or regional inventory system for blood products and blood doners. If workable, such a system would insure more equitable distribution of blood and blood products, forestall the development of local shortages through redistribution of temporary surpluses, minimize whole blood losses through outdating, and serve many other useful purposes.

The $2,792,000 available in 1968 and requested for 1969 will support the continuation of committed studies and the new projects proposed.

## Heart Cooperative Drug Study

This is an Institute coordinated program to determine whether several lipid-lowering drugs will reduce the incidence of recurrent attacks and increase longevity among heart-attack victims. Most of the funding of this study is by research grants to approximately 55 participating clinics. Ancillary funds included under Collaborative Research and Development are for reimbursement to other Public Health Service units for performing the required laboratory determinations and for ordering, packaging, and distributing the necessary drugs.

There are also increases for Collaborative Research and Development of $6,000 for annualization of the 1968 pay increase partially offset by a $2,000 decrease for centrally furnished services from the "National Institutes of Health management fund."

## Biometry, Epidemiology, and Field Studies

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 83 | $958,000 | 83 | $974,000 | -- | +$16,000 |
| Other expenses | | 789,000 | | 791,000 | | +2,000 |
| Total | 83 | 1,747,000 | 83 | 1,765,000 | -- | +18,000 |

This activity conducts direct studies and also participates in cooperative studies in cardiovascular research. The major thrusts of this program are in epidemiology, geographic pathology, biostatistics, and the clinical evaluation of therapeutic agents. This program provides a valuable mechanism not only for undertaking direct research in selected scientific areas, but also for collaboration with grantees, intramural research scientists, and foreign research workers conducting investigations of program interest.

As in other parts of the National Heart Institute, the collaborative studies program balances studies of relatively immediate clinical relevance with those of a more fundamental, long-range nature. Thus, the staff conducts or collaborates in epidemiologic research where "experiments of nature" have resulted in unusually high (or unusually low) rates of cardiovascular diseases, with the purpose of identifying those risk factors that may be responsible for such differences. Also, the program assists in the development of clinical trials to study the effectiveness of drugs, diet, or other factors which may be effective in reducing heart diseases. It is estimated that 70 percent of the funds in this activity are allocated to such clinically relevant studies. The remaining activities are of a more fundamental character and deal with the design and analysis of studies and the development of new biomathematical methods for biological research.

Included in the increase is $16,000 for mandatory items such as annualization of the 1968 pay increase and the one extra day of pay in 1969. There is also an increase of $2,000 for centrally furnished services from the "National Institutes of Health management fund."

Direct Training

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 12 | $107,000 | 12 | $109,000 | -- | +$2,000 |
| Other expenses..... | | 115,000 | | 115,000 | | --- |
| Total..... | 12 | 222,000 | 12 | 224,000 | -- | +2,000 |

Incorporated in this program is the training of Public Health Service personnel to meet the long-range and immediate scientific personnel needs of the Institute and the Service. This is an important and basic part of the heart research program in that it provides for the training of qualified investigators who must keep abreast of new knowledge, techniques, and methods that are constantly being developed so that they may function at the highest level of proficiency in the cardiovascular research effort.

The $2,000 increase requested provides for annualization of the 1968 pay increase.

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 105 | $1,021,000 | 110 | $1,070,000 | +5 | +$49,000 |
| Other expenses..... | | 1,474,000 | | 1,541,000 | | +67,000 |
| Total..... | 105 | 2,495,000 | 110 | 2,611,000 | +5 | +116,000 |

This activity provides for assembling, processing, and reviewing all cardiovascular grant applications; support of the National Advisory Heart Council and special review committees and consultants; grant tabulation and analyses; and the scientific and administrative management of grants.

Of the $116,000 increase requested $35,000 and 5 positions will provide for additional analytical and reporting functions. Also included is $18,000 for such mandatory increases as the annualization of the 1968 pay increase and the one extra day of pay in 1969. There are also increases of $63,000 for centrally furnished services from the "National Institutes of Health Management Fund".

Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 31 | $274,000 | 31 | $279,000 | -- | +$5,000 |
| Other expenses | | 524,000 | | 560,000 | | +36,000 |
| Total | 31 | 798,000 | 31 | 839,000 | -- | +41,000 |

This activity supports the over-all administration, coordination, and direction of the varied programs and activities of the Institute. The Director and his immediate staff are responsible for introducing new knowledge into current operating programs and for the planning, development, and review of new areas of focus and interest.

Of the $41,000 increase requested, $19,000 will provide for additional program planning within the Institute and for ad hoc review groups. Also included is $5,000 for such mandatory increases as the annualization of the 1968 pay increase and the one extra day of pay in 1969. There are also increases of $17,000 for centrally furnished services from the "National Institutes of Health Management Fund".

WEDNESDAY, MARCH 20, 1968.

# NATIONAL INSTITUTE OF DENTAL RESEARCH

## WITNESSES

DR. SEYMOUR J. KRESHOVER, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
HERBERT C. CHRISTOFERSON, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
DR. RICHARD C. GREULICH, DIRECTOR OF INTRAMURAL RESEARCH, NATIONAL INSTITUTE OF DENTAL RESEARCH
MRS. FRANCES H. PETTINATO, BUDGET OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

### OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 2,659 | 2,903 | 3,007 |
| Positions other than permanent | 28 | 30 | 30 |
| Other personnel compensation | 26 | 32 | 32 |
| Total personnel compensation | 2,713 | 2,965 | 3,069 |
| Personnel benefits | 320 | 337 | 347 |
| Travel and transportation of persons | 120 | 130 | 148 |
| Transportation of things | 33 | 30 | 36 |
| Rent, communications, and utilities | 75 | 97 | 101 |
| Printing and reproduction | 13 | 35 | 35 |
| Other services | 202 | 312 | 338 |
| Project contracts | 495 | 629 | 629 |
| Services of other agencies | 186 | 200 | 200 |
| Payment to "National Institutes of Health management fund" | 1,404 | 1,534 | 1,601 |
| Supplies and materials | 352 | 370 | 394 |
| Equipment | 262 | 230 | 271 |
| Grants, subsidies, and contributions | 22,048 | 23,057 | 23,250 |
| Subtotal | 28,223 | 29,926 | 30,419 |
| Quarters and subsistence charges | −5 | −5 | −5 |
| Total obligations | 28,218 | 29,921 | 30,414 |

### PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 310 | 322 | 329 |
| Full-time equivalent of other positions | 5 | 5 | 5 |
| Average number of all employees | 292 | 308 | 315 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 15,098 | 15,617 | 15,626 |
| (b) Fellowships | 1,552 | 1,971 | 2,015 |
| (c) Training | 5,398 | 5,469 | 5,609 |
| Total, grants | 22,048 | 23,057 | 23,250 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 3,980 | 4,541 | 4,740 |
| (b) Collaborative research and development | 783 | 841 | 844 |
| (c) Biometry, epidemiology, and field studies | 424 | 432 | 435 |
| (d) Review and approval of grants | 618 | 647 | 706 |
| (e) Program direction | 390 | 403 | 439 |
| Total, direct operations | 6,195 | 6,864 | 7,164 |
| Total, program costs, funded [1] | 28,243 | 29,921 | 30,414 |
| Change in selected resources [2] | −25 | | |
| Total obligations | 28,218 | 29,921 | 30,414 |
| Financing: | | | |
| Comparative transfers from other accounts | −151 | | |
| Unobligated balance lapsing | 229 | 367 | |
| New obligational authority | 28,296 | 30,288 | 30,414 |
| New obligational authority: | | | |
| Appropriation | 28,308 | 30,307 | 30,414 |
| Transferred to other accounts | −12 | −19 | |
| Appropriation (adjusted) | 28,296 | 30,288 | 30,414 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 28,218 | 29,921 | 30,414 |
| Receipts and other offsets (items 11–17) | −151 | | |
| Obligations affecting expenditures | 28,067 | 29,921 | 30,414 |
| Obligated balance, start of year | 15,086 | 18,345 | 23,167 |
| Obligated balance, end of year | −18,345 | −23,167 | −28,481 |
| Adjustments in expired accounts | −493 | | |
| Expenditures | 24,315 | 25,099 | 25,100 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 11,397 | 9,207 | 6,000 |
| Out of prior authorizations | 12,918 | 15,892 | 19,100 |

[1] Includes capital outlay as follows: 1967, $197,000; 1968, $230,000; 1969, $271,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $876,000; 1967, $852,000; 1968, $852,000; 1969, $852,000.

Mr. FLOOD. We now have the National Institute of Dental Research, and the presentation will be made by Dr. Kreshover, Assistant Surgeon General and Director of the National Institute of Dental Research.

We will insert your biographical sketch at this point in the record.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

(Biographical sketch follows:)

BIOGRAPHICAL SKETCH

Name: Seymour J. Kreshover, Assistant Surgeon General.
Position: Director, National Institute of Dental Research.
Birthplace and date: New York, N.Y., June 22, 1912.
Education:
Syracuse University, Liberal Arts College.
New York University, Liberal Arts College—B.A.—1934.
University of Pennsylvania, School of Dentistry—D.D.S.—1938.
Yale University (clinical medicine and pathology)—Ph. D.—1942.
New York University, School of Medicine—M.D.—1949.
University of Buffalo—(Hon.) Doctor of Science—1961.
University of Pennsylvania—(Hon.) Doctor of Science—1967.

Experience:
1966: Director, National Institute of Dental Research, National Institutes of Health.
1956–66: Associate Director (In Charge of Research), National Institute of Dental Research, National Institutes of Health.
1956: Visiting professor of dental research, the Medical College of Virginia.
1956–60: Associate trustee, board of medical education and research, University of Pennsylvania.
1949–56: Professor of oral pathology and diagnosis, director of dental research, director of graduate and postgraduate studies, the Medical College of Virginia, Richmond.
1946–48: Private dental practice (part time).
1946–47: Teaching fellow in histoanatomy, New York University.
1942–46: U.S. Army Dental Corps. 39th General Hospital (affiliated Yale unit), chief of dental service.
1942–43: Assistant in oral surgery, Yale University School of Medicine.
1938–39: University fellow, University of Illinois Graduate School.
Association memberships:
American Dental Association.
American Medical Association.
Federation Dentaire Internationale.
International Association for Dental Research.
American Association for the Advancement of Science (fellow).
American College of Dentists (fellow).
American Public Health Association (fellow).
Diplomate, American Board of Oral Medicine.
Honorary member, the New York Institute of Clinical Oral Pathology, Inc.
Consultant to Council on Dental Research, American Dental Association.
Consultant to Committee on Research, American College of Dentists.
1961–67: Chairman, Commission on Dental Research, Federation Dentaire Internationale.
1962: President, International Association for Dental Research.
1963–66: Secretary, Section Nd (Dentistry), American Association for the Advancement of Science.
Special awards, citations, or publications:
1945: Commendation Award for Especially Meritorious Service with Western Pacific Base Command.
1960: Recipient of Tufts University Award for Leadership in Oral Pathology.
1965: Recipient of the Alumni Research Award Medal, the Association of Dental Alumni, Columbia University.
1965: Recipient of the Public Health Service Meritorious Service Medal.
Author of some 50 publications.

Mr. FLOOD. I see you have a statement here as well.

How do you wish to proceed with it?

Dr. KRESHOVER. I would like at this time to read my statement and then respond to questions or further clarification of any point I make briefly in my formal statement.

## GENERAL STATEMENT

Dr. KRESHOVER. Mr. Chairman and members of the committee, I am happy to have this opportunity to appear before you again. This year marks the 20th anniversary of the National Institute of Dental Research. Like a mosaic being pieced together, the bits of new information garnered over these two decades have made the whole problem of oral disorders more comprehensible, and thus more amenable to attack.

DENTAL CARIES

One of our most promising current achievements is in the field of dental caries, or tooth decay. The search for causative microorganisms has now narrowed down to specific anaerobic streptococcal bacteria with certain unique distinguishing characteristics.

Mr. FLOOD. What is an anaerobic streptococcal bacteria?

Dr. KRESHOVER. An anaerobic streptococcal bacteria is a streptococcal organism that grows in the absence of oxygen whereas an aerobic streptococcus is an organism that requires oxygen for its growth. These are certain cultural characteristics that distinguish the particular kind of bacteria that are involved in dental decay. An especially significant property is the ability of the bacteria to produce and surround themselves with a gummy polysaccharide. This extracellular coat appears to be responsible for the bacteria's adherence to the tooth as microbial plaque. In collaborative research we have found that a specific enzyme, when given to animals in food and water, breaks down this dextran polysaccharide and almost completely prevents plaque formation and decay. We hope to initiate controlled clinical trials in the near future. If they bear out earlier findings, this enzymatic treatment may prove to be a real boon to preventive dentistry.

I might add, Mr. Flood, that this is a finding in the course of the past several months that we are particularly excited about, and I would like to clarify this at a later time, if you wish.

FLUORIDE

Following the demonstrated success of water fluoridation, we are further exploring the use of fluoride through other means in order to bring this benefit to those populations not having access to fluoridated communal water supplies. The use of a fluoride gel topically applied in fitted mouthpieces continues to be promising.

Still in a preliminary stage, a new technique seals the pits and fissures in the grinding surfaces of teeth with a plastic mixed with fine silica particles. Of potential importance, particularly to children whose carries risk is high, the adhesive wears off in time but reportedly gives excellent protection against tooth decay for as long as 6 months.

PERIODONTAL DISEASE

In studies related to periodontal disease, work has now progressed to the point where we can begin to determine the specific composition and arrangement of the polypeptide or amino acid chains that make up the collagen molecule; it being the principal structural component that attaches or fixes the tooth in its bony socket. Since collagen constitutes a principal structural component of the periodontal tissues, these findings suggest that defects in the collagen molecule, probably associated with periodontal disease, may be susceptible to correction through such means as nutrition and not involve more complex genetic alterations.

Also, during this year, and for the first time, so-called hyaluronidase, an enzyme kind of activity has been demonstrated in diseased human gingival tissue. This is significant because hyaluronidase is known to be antagonistic to the jelly-like hyaluronic acid that is a component of

the cementing substance between fibers of the normal gingivae. Recent studies have also provided experimental support for the concept of sensitization and allergic response in periodontal disease. Thus, it has been shown that tissue-bound immunoglobulins are abundant in inflamed human gingiva but not in normal gingiva, and that gingival inflammation similar to that seen in humans can be produced in animals by local treatment with allergens.

### ORAL ULCERATIONS

Institute scientists have also recently found that a virus can combine with its antibody without losing infectivity. This finding helps to explain the persistence in some patients of certain viral diseases such as herpes labialis (fever blisters) despite the presence of high levels of antibody in their sera.

You recall a year ago or so you queried one of your witnesses appearing before you on this very troublesome malady of man.

### ORAL CANCER

In oral cancer, the research focus is on the detection of subtle changes in the oral mucosa that may lead to cancer. Certain irritants are implicated in preliminary research findings that suggest a correlation between a condition known as submucous fibrosis and cancer. Studies on oral cancer will be expanded because of the magnitude and severity of this problem. I will be happy to expand on this later on if you wish, Mr. Flood.

### DENTAL RESTORATIONS

Efforts in the areas of dental restorations are directed toward the development of a broad spectrum of materials, ranging from adhesive fillings to prostheses for persons disfigured by oral-facial injury or cancer. Approaches are equally diversified, ranging from studies of the adhesive properties of barnacle cement to observations of plastic tooth implants in experimental animals. And again you recall last year you referred to this with some considerable interest as related to prizefighting.

### CLEFT PALATE

Recent progress in the study and treatment of cleft palate is covered in a special report submitted to your subcommittee, Mr. Flood. In a related area of study, it has been shown recently that the individual who suffers from a congenital retardation of tongue growth and function can compensate to the point of achieving excellent speech articulation.

### RESEARCH INSTITUTES

To provide a further stimulus to basic and clinical investigations of the oral disorders, five broad-based research institutes are now in varying stages of development at the Universities of Washington, Pennsylvania, Alabama, Michigan, and North Carolina. Strong interest in establishing such interdisciplinary centers has also been evidenced by four other universities or university consortia on a regional basis.

Mr. Chairman, gratifying progress against oral diseases is further reflected in the research highlights. Significant efforts are being pursued in the training of promising young people to make available the scientific manpower resource so essential for continued progress.

Again I would be so presumptuous as to suggest we are so concerned about the manpower program in our dental schools that I would be very happy to respond to questions at the appropriate time if you wish to query me further on this matter.

We are requesting a budget for 1969 or $30,414,000, an increase of $493,000 over the 1968 operating level of $29,921,000. Included are increases of $184,000 for training grants and fellowships, $199,000 for laboratory and clinical research, $59,000 for review and approval of grants, and $36,000 for program direction. We will operate at about the same level in research grants, collaborative research and development, and biometry, epidemiology, and field studies.

Mr. Chairman and members of the committee, this concludes my formal statement.

Mr. FLOOD. This shop of yours has been operating 20 years?

Dr. KRESHOVER. Yes, sir; this is our 20th anniversary this June. I believe very notable progress has been made during that period of time.

We would be very happy to expand on any of the points that we made briefly.

PUBLIC IMAGE OF NATIONAL INSTITUTE OF DENTAL RESEARCH

Mr. FLOOD. I am sure of that. Does it occur to you that this particular Institute has been hiding its light under a bushel as compared to some of the others for some 20 years? We hear so much in the news media about the various component institutes of NIH, but very little about dental research. Why would that be? Do you not have a good press agent in your shop?

Dr. KRESHOVER. Yes, sir; I believe that we have one of the very best. Our information office during the course of the past 2 years has done a truly magnificent job.

Mr. FLOOD. In the last 2 years?

Dr. KRESHOVER. Yes.

Mr. FLOOD. It is about time.

Dr. KRESHOVER. That is since Mrs. Brocard came on with us.

I might say in further clarification of my answer to your question, the environment at the National Institutes of Health is most unique insofar as dental research and relevant educational enterprises in support of dental research are concerned. I say unique because it is a part of the total effort, it is a part of the total campus, it is an expression in our research activities of, I think, the truest kind of example of collaborative efforts.

Mr. FLOOD. The impression is that you are low man on the totem pole.

Dr. KRESHOVER. No, sir; far from it. This impression might very well be one of dentistry in toto, as represented particularly by the dental schools and by the national level of support of dental education.

At NIH during my period of 10 years now—and I do not say this because of present company—I most sincerely say that I never worked in an environment where there has been the kind of support for dental

activities that there has been at the National Institutes of Health. This is the principal reason I continue to be there.

On the outside, on the other hand, I do feel that we are very much concerned about our dental schools and it is part and parcel, I am sure, of the query you make of me now. Dental schools are, many of them, in very dire financial straits at this time. Particularly our private institutions. We find, for example, that—and I believe Surgeon General Stewart in his testimony before you called attention to the fact—at least one of our dental schools has already indicated the need to close its doors. Other dental schools are on the way.

Mr. FLOOD. That one we probably cannot do much about.

Dr. KRESHOVER. This again is part of the meaning of your very question. Unfortunately, I do not think the public has yet gained proper appreciation of the importance of dental education and dental research efforts as a part of the community of effort outside. At the NIH I am happy to say they do.

Mr. FLOOD. That is fine, but the public only knows what is presented to it. If the case is not being presented, the public will not know about it and will not go looking for it.

Dr. KRESHOVER. It is interesting to recall though, Mr. Flood, that in the support of dental education and dental research efforts outside, of some 4,000 philanthropic foundations listed, for example, in "American Philanthropic Foundations and Their Fields," only six, as I would recall it, even mention dentistry as an area of interest.

Mr. FLOOD. Why?

Dr. KRESHOVER. Again I would believe that it is a matter of dentistry today being at an important crossroads in its history.

I believe at this time we see a joining of forces with the broad base of biology and medicine, and that dentistry is becoming a part of the mainstream of biology and medicine. I am very optimistic that with proper support, which I think must be forthcoming, dentistry will indeed come into its own as a true part of academic medicine.

Mr. FLOOD. It is odd the profession would not make an effort in a major way to bring this to the attention of these 4,000 institutions.

Dr. KRESHOVER. They are trying desperately.

Mr. FLOOD. Desperately?

Dr. KRESHOVER. Yes, sir; they are. The contributions of Dr. Hillenbrand who sits at the helm of the American Dental Association. Through his imaginative and vigorous leadership, the American Dental Association again in recent years has been doing much.

Mr. FLOOD. How recent, 2 years?

Dr. KRESHOVER. I do not think I would be in a position to define the span of this effort. It has been remarkable.

### SUMMARY OF BUDGET REQUEST

Mr. FLOOD. You are asking $30,414,000 for 1969. That is only $107,000 more than the appropriation for 1968 before the application of H.J. Res. 888. Making the comparison after the cut by H.J. Res. 888, the increase is only about 1.5 percent.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. That is not going to allow you any dramatic increase in your program, will it?

Dr. KRESHOVER. No, sir; far from it. We believe that under these times of stringent budget, and we are most understanding of the need for this, that we must establish priorities. Certain programs that are relatively of great importance must perhaps be made to hold the line. But we trust that with our budget as it is, we might through careful planning at least keep a head of steam up and move forward. We dare not go backward.

RESULTS OF PROGRAM REDUCTION

Mr. FLOOD. You are a rare bird; we have been sitting here a long time and do not hear much talk like that. According to the justifications, this budget for 1969 will support nine fewer research grants, five fewer fellowships, one less training grant. What will be the practical results of this reduction on your program?

Dr. KRESHOVER. There are several program areas that we feel are critical to our continuing contributions to the broadening base of the dental sciences and relevant education. The net effect, without being able to single out by identification isolated projects in terms of example, will be one of not certainly being able to accelerate or move as fast as we would like to in the broad array of support of research and training; in our direct operating program; and indeed in our collaborative contract research.

So all of our programs will obviously have to take a fair share of the burden. But, as I indicated to you earlier Mr. Flood, through appropriate identification and establishment of priorities, we hope to move forward and not regress.

DENTAL RESEARCH INSTITUTES

Mr. FLOOD. You have five dental research institutes in various stages of development. You say on page 102:

> It is expected that two or possibly three more centers will be initiated in 1968 and in 1969.

How would you do this when you have exactly the same amount of funds, $3 million, budgeted for 1968 and for 1969 as you had in 1967?

Dr. KRESHOVER. As you pointed out, to date the National Institute of Dental Research has awarded support for the establishment of five institutes. Taking off at a comparable stage of early planning and development, the additional institutes that we envisage coming into being will do so at the expense of what we call nonrecurring costs incurred in the first year of the development program in the established five institutes.

The additional institutes, then being funded as a consequence of nonrecurring cost savings in the already established institutes, will obviously have to take off at a very modest level of support.

ORAL CANCER

Mr. FLOOD. You mentioned, in your affirmative statement, oral cancer. What is the demarcating line between you and the Cancer Institute in activities in the field of oral cancer?

Dr. KRESHOVER. We have established with the National Cancer Institute, as well as with other institutes where we have programs in

parallel, rather clear guidelines on the parameters of our responsibilities and the other institutes. These are established on the basis of rather formal agreements so that the project officers at the National Institutes of Health receiving applications from prospective grantees in the field will have appropriate guidelines and recognize where these must be channeled. In the case of our responsibilities in the field of oral cancer, these guidelines are quite well established.

We are concerned with cancer in and about the mouth involving the lips, involving accessory structures to the oral cavity, and it is an effort that we are beginning to accelerate within the scope of——

Mr. FLOOD. I know that, but where is the dividing line? How do you know where you are and how do they know where they are?

Dr. KRESHOVER. The dividing line is most simply stated as a geographic one, a geographic one as related to body systems. We are concerned with the oral tissues. I must say that our programs, whether they be in the cancer field or in the field of studies of skeletal tissues, are accomplished in close harmony with the other institutes. We know what our responsibilities are and the Cancer Institute recognizes what our particular competencies are.

### RESEARCH ON PEOPLE WITHOUT DENTAL CARIES

Mr. FLOOD. I see practically nothing in your justifications about research on the 1 or 2 percent of the people who are immune to dental cavities; caries, as you call them. That would seem to be a very fruitful field to enter, would it not?

Dr. KRESHOVER. Yes, sir. While our statement might not have included this for reasons of brevity, we have been and are indeed very much concerned about exploiting this particular direction of research.

Mr. FLOOD. Two percent of the people are immune to cavities?

Dr. KRESHOVER. Yes, sir.

Dr. SHANNON. Let's not say they are immune; they do not have them.

Dr. KRESHOVER. Dental caries is a very complex disease. It is constituted of three broad factors which must all be present at one and the same time in order for the lesion to be developed, to be initiated. These three factors are the bacterial component, the dietary component, and what we call the host resistance and host susceptibility component. This is the systemic factor.

A small percentage of the population is caries resistant, shall we say. Incidentally, animals also can be bred in colonies to demonstrate this kind of resistance to the disease and provide us with a new unique tool because it will further clarify the genetic factor involved, we hope.

Mr. FLOOD. Suppose you found it. Would that be merely an academic interest, or does this enter into the field of prophylactics? Could you make it 10 percent?

### FLUORIDATION

Dr. KRESHOVER. Certainly, the contribution, as you well know, that has been made to the control of dental caries through the utilization of water fluoridation has now provided us with a 60-percent reduction in dental caries. Extending in this direction, we in the course of just recent months, as again indicated in my opening statement, have come upon some very exciting findings.

Mr. FLOOD. I was going to ask you about that. We will put those two together.

Do you have anything very exciting to report about fluoridation, insofar as it being a preventive of tooth decay, since you were here last?

CHEEKTOWAGA STUDY

Dr. KRESHOVER. Since we were here last, we have extended our researches in the area of the topical application of fluoride in the control of dental caries. We can now report to you on our one community study now at the point of completion of 2 years of observation; this being in Cheektowaga, N.Y., just outside of Buffalo.

Mr. FLOOD. Why would you pick that town—just off the left field fence?

Dr. KRESHOVER. It was not off the left field fence. It has had several important elements that made its selection important to us. One was that it is a community that has a low level of naturally occurring fluoride in its water.

Mr. FLOOD. Is that uncommon?

Dr. KRESHOVER. No; it is not particularly uncommon. It is an area that has not yet been fluoridated and it was important in our experimental approach to have an opportunity to observe young children so that the effects of what we call a topical application of this fluoride with a technique that has been developed by our Institute scientists would not be camouflaged by another factor.

In addition to meeting this important criterion, there is a dental school that is one of the components of the State University of New York at Buffalo.

Mr. FLOOD. Is that nearby?

Dr. KRESHOVER. Yes, sir. Cheektowaga is a suburb of Buffalo. We have the opportunity of expertise there. We also have the opportunity for a carefully controlled study in a selected school population.

Dr. SHANNON. And it is the right size.

Mr. FLOOD. What do you mean by size; population?

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. What is the population of the town?

Dr. KRESHOVER. I do not know the population of the town. I can tell you the student population, which was approximately 500. These being young boys and girls aged 11 to 14, with the opportunity under this kind of careful supervision made possible in the community school system in this suburban area to launch our study.

Mr. FLOOD. You get good cooperation there?

Dr. KRESHOVER. Excellent cooperation, and this is an important ingredient.

Mr. FLOOD. Is there not a like town with a like school population in three or four other parts of the country?

Dr. KRESHOVER. There is no question that there is. As a matter of fact, this is a beginning. We have to take off from some beginning point. At the present time this study is being duplicated in Charlotte, N.C.

Mr. FLOOD. You have been at this 2 years in this town?

Dr. KRESHOVER. Two years in the Buffalo suburban area. And recently begun about a year ago in Charlotte, N.C. The study there now takes off from a different base. This is a community that is fluoridated.

Now we are interested in seeing whether the results in Cheektowaga, which represented an 80-percent reduction in dental decay in school-children, will be augmented in the Charlotte, N.C., study because of the very presence of fluoride in the water.

Mr. FLOOD. Is the New York town suburban Buffalo or upstate rural New York?

Dr. KRESHOVER. Suburban Buffalo.

Mr. FLOOD. And Charlotte is a middle-sized city?

Dr. KRESHOVER. Yes, sir.

### RESEARCH ON EFFECT OF BACTERIA

With your indulgence, Mr. Flood, I might say a few more words about another area of our efforts to advance our knowledge in the field of dental caries, and this is the evidence, to date, of the important component of bacteria in the causation of the lesion. There is evidence now that these bacteria require a particular kind of sugar, sucrose, in order to develop the gummy substance-polysaccharide, so-called, that I referred to in my opening statement. This then is responsible for the very rigid attachment of what we call a plaque to the smooth surface of the tooth so that the action of the bacterial organisms on the food-stuffs contained within the plaque, with the production of acid, can initiate the lesion. It is the interest in this area that has recently prompted the establishment of what we elected to identify as a caries task force to accelerate this organized program research effort which is federally initiated.

It is a program that took off from the base of our direct operating program within our institute, and is now being extended.

### OPPOSITION TO FLUORIDATION

Mr. FLOOD. In this whole area of fluoridation of water for human consumption, you have been meeting with more or less widespread and certainly dedicated opposition to this program?

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. Why? Why would they object; why would they be opposed to this program? I know all the reasons that have been given. But why do you think?

Dr. KRESHOVER. The reasons were, I believe, very adequately stated last year when you addressed the same question to me and at that time, in recalling the record, Dr. Shannon made some very critical points that I would hope, with your agreement, would be entered into the record again, with perhaps further expansion this time. The reasons continue to be the same.

Mr. FLOOD. Yes; I know that, but why do you think it started in the first place? How did it ever assume the proportions that it did?

Dr. KRESHOVER. Rather misguided persons who seek to identify themselves with a sense of mission, a sense of dedication in an enterprise that is ill-conceived, that perhaps is based on an opportunity to find themselves on a bandwagon to make assessments. These, unfortunately, have thrust a number of people in the position where they envisage themselves perhaps as community leaders leading a parade in the public interest. These are misguided people by and large.

Mr. FLOOD. They are very vocal, you know.

Dr. KRESHOVER. Yes, sir; they are. But I would have you recall, as Dr. Shannon reminded you and your subcommittee members a year ago, that the same kind of opposition has been experienced throughout the history of medicine in other fields as well.

Mr. FLOOD. How would there be any shifting of allegiance in this program of fluoridation? Why would a person of some scientific or dental or medical background, who at one time was carrying a torch for fluoridation, wake up one morning and find out he was on the other side?

Dr. KRESHOVER. Mr. Flood, I must be very candid and express some disagreement with this observation insofar as I believe the direction has been quite the reverse. Individuals with medical experience and professional experience in the field of biology have reversed themselves and now support fluoridation. I am not aware of what I would certainly agree might be some exceptions of the situation you call to my mind. I do not think it has quite been in that magnitude, Mr. Flood. I really do not.

Mr. FLOOD. Are you in a position to know?

Dr. KRESHOVER. Most certainly I would be in a position to document and provide for the record instances of the kind of oppositions to fluoridation led by individuals who have professional credentials, but at the same time I would elect also to provide for the record the qualifications and the contributions made by those who have endorsed and have supported fluoridation, and I think their credentials will speak for themselves.

CLEFT PALATE

Mr. FLOOD. Do you have anything more to tell us this morning about cleft palate?

Dr. KRESHOVER. Yes, sir. This is an area we have been very active in. As you will recall, Mr. Flood, a cleft palate continues to constitute one of the major physical disabilities known to man. Indeed, of all of the congenital malformations that afflict our population, cleft palate and cleft lip represent about 14 percent of the total.

The number of live births that would find expression in an individual with cleft palate and/or cleft lip numbers 1 in 750. So we are very much concerned about this anomaly, and our program efforts have largely taken off in two general directions: One is to learn more about cause. The other one is to learn more and make more meaningful contributions to methods of rehabilitation, of repair, of correction involving speech——

Mr. FLOOD. It is a congenital condition?

Dr. KRESHOVER. Oh, yes. It is congenital insofar as appearing in the newborn.

Mr. FLOOD. Are you concerned about the prenatal condition? Could you correct that, or are you more concerned about the ex post facto conditions?

Dr. KRESHOVER. We are concerned in both areas.

Mr. FLOOD. What would you do about treatment?

Dr. KRESHOVER. While we are concerned about treatment and concerned about correction, the ultimate solution to any problem is going to be in its prevention. So our principal objective now is to learn more

about cause, and through understanding the mechanisms of disease, then have appropriate methods for their prevention.

In the case of cleft palate and cleft lip, we have good reason to believe today that about 20 percent of these abnormalities are genetic or hereditary.

Mr. FLOOD. Would that not be quite a trick to isolate this and to prevent it?

Dr. KRESHOVER. Yes, sir; it may well be a trick. On the other hand, we believe that in addition to the genetic component, the hereditary factor, there are a number of environmental factors. Our approaches to the study of etiology or cause have largely been related to the utilization of animal model systems in the laboratory. In the laboratory we can very adequately define a number of environmental factors that are operating during the time the fetus is in the mother's uterus.

We do considerable research with mice and rats and hamsters in our laboratory efforts to better understand the mechanisms of this disability.

Mr. FLOOD. But you do not know much now?

Dr. KRESHOVER. We know more than we knew yesterday, and yesterday we knew more than we did before that time.

I would say that most of our significant findings in the field of cleft palate, to date, so far as the clinical approaches are concerned, have been in new surgical techniques, new methods of repair.

Mr. FLOOD. That is repair and correction?

Dr. KRESHOVER. Yes, sir. These have been significant contributions and we believe now we know more, Mr. Flood.

Mr. FLOOD. Is cleft palate more common in certain areas of the country than it is in others?

Dr. KRESHOVER. The question you raise is a most interesting one because we know today that there are two kinds of cleft palate. The cleft lip alone or the cleft lip with or without cleft palate is a separate entity that probably is genetic.

Mr. FLOOD. That is not responsive to my question.

Dr. KRESHOVER. It will be in a moment, Mr. Flood, because we find, for example, that cleft palate and cleft lip when they are in combination, or cleft lip alone, which is largely a genetically determined disease, are found in certain population groups. The American Indians, for example, have a much higher incidence of cleft palate than do, for example, Caucasians and Negroes. The Japanese have a particularly significantly higher incidence of cleft lip and palate, which is genetically determined, than do the Caucasians.

Mr. FLOOD. What about the rural areas as distinguished from urban areas?

Dr. KRESHOVER. I know of no geographic relationship insofar as States or communities are concerned with specific reference to this question. Certainly on an ethnic background basis, there is a geographic relationship. Beyond this I confess I do not know.

Mr. FLOOD. We will place your special report on cleft palate in the record.

(The report follows:)

SPECIAL REPORT:
CLEFT PALATE AND RELATED SPEECH DISORDERS

Cleft palate, with or without cleft lip, is one of the most common malformations, afflicting approximately one out of every 800 babies born alive in the United States. A severe cleft makes swallowing and speaking difficult, increases the danger of ear infections and deafness, brings psychological problems, and usually burdens the family financially. Therefore, the National Institute of Dental Research conducts research into causes of this defect and ways to improve treatment. The Institute also supports research in other institutions throughout the country. Among these are a number of centers where treatment and research encompass all of the cleft problems of each child. It is necessary to develop better methods of surgical repair and speech therapy so that afflicted children may live as normally as possible, but the ultimate goal is prevention of those clefts which are caused by environmental hazards.

Definition of Clefts

Long before birth the tissues that will compose the palate and lips form on each side of the head, grow, turn toward each other, meet, and join. Finally, a complete palate forms a shelf between the nose and the mouth. Whenever necessary in eating and speaking, the soft palate, the walls of the throat, and the tongue move in concert to block, completely, the opening between the nose and the mouth. In eating and speaking, the lips and tongue also cooperate to open and close the mouth. When parts of lip or palate fail to join, there is a cleft which usually disturbs these vital functions.

The cleft or hare lip, although more disfiguring, is usually easier to correct than the cleft palate. Sometimes both the lip and palate clefts are widely gaping, and sometimes the defect may be a mere blemish, i.e., a slight pit in the lip, or a crack hidden under the covering membrane of the palate.

A cleft lip, occurring with or without a cleft palate, seems to be a different disorder from cleft palate alone, but the causes of both types are obscure. More than one cause seems to operate in both malformations. Cleft lip occurs about three times as often in Caucasians as the isolated cleft palate, and heredity (perhaps of many genes) is more often implicated than in cleft palate alone.

Sometimes environmental factors clearly link with the defect, as, for instance, when cleft offspring are born to animals after administration of certain drugs during pregnancy. More than one cause may operate even in a single case. Individual susceptibility may require an unfavorable environment to interfere with the joining process. The fact that mothers of cleft babies miscarry more often

than other mothers, or that clefts, like other defects, are more common among the poor, may be due to multiple causes.

To learn the various causes of oral-facial clefts, researchers take many approaches, including studies of heredity, of spontaneous clefts in laboratory animals, and the metabolism of various drugs and chemicals known or suspected to be associated with clefting.

Inheritance of Clefts

Institute scientists studying the genetic background of clefting among American Indians report that isolated cleft palate occurs with equal frequency among Indians and Japanese, and about twice as frequently in them as among Negroes and Caucasians. On the other hand, cleft lip (with or without cleft palate) is less common among Indians than among Japanese, but more common among Caucasians, and considerably more so among Negroes.

In another Institute analysis, 93 Caucasian families having children with clefts seen at the Lancaster Cleft Palate Clinic were compared with 82 similar families with children seen at this Clinic for other dental and speech problems. Comprehensive family pedigrees and medical histories were recorded, with special attention to the occurrence of other noticeable congenital abnormalities.

In this study, isolated cleft palate was equally common in both sexes. In those families in which some other member had a cleft, the inheritance could be traced through only one side of the family. This inheritance pattern suggests the action of a dominant gene.

In contrast, some 72 percent of the cases of cleft lip (with or without cleft palate) were male. Moreover, those individuals who had cleft relatives apparently inherited the defect from both sides of the family, as would be expected with recessive genes or multigenic inheritance. Both types of clefts occasionally appeared as mild abnormalities such as a lip notch or a forked uvula.

The investigators found no significant differences in number or timing of pregnancies, age of parents, or birth rank when comparing families with and without clefts. On the other hand nearly twice as many serious congenital malformations occurred in various organ systems in families with both types of clefts as in families without clefts.

Somewhat similar studies of all Icelandic children born with clefts between 1956 and 1962 showed that one baby out of each 515 births had a cleft. This is the highest rate known for Caucasians, and may reflect the excellence of Icelandic record keeping or perhaps the fact that being somewhat isolated, the population is rather inbred. Nearly 60 percent of the children observed with cleft lip

(with or without cleft palate) were boys, whereas isolated cleft palate occurred twice as often in girls. Also, babies with all types of clefts are twice as likely to be premature as other babies. Further observations were: The more frequent incidence of clefts in the third child; the rarer occurrence of clefts in children born in summer as compared with those born in the fall; and the likli-hood of mothers of cleft children to be either under 20 years of age or between 30 and 34 years.

Study by an Institute grantee of the inheritance of a very rare trait seen as pits or fissures in the lip also sheds light on the genetic patterns of clefts in lips and palates. The rarity of familial lip pits necessitated international cooperation to make a statistically valid study of inheritance of this condition. The trait is dominant but not always visibly expressed. It sometimes occurs alone and sometimes accompanies frank clefts of lip or palate. Individuals with both pits and clefts are quite likely to have cleft offspring, so it is fortunate that only one in over 75,000 is af-fected by this gene.

Another rare, but much more distressing defect, the Pierre Robin syndrome, combines cleft palate with a very poorly developed lower jaw. Children with this condition have great difficulty in breathing and swallowing. A recent Institute-supported study of a human fetus indicates that clefting in these cases probably occurs because a normal-sized tongue is positioned by an abnormally small jaw so that it must push into the nose. The pressure of the tongue then keeps the two sides of the developing palate from growing to-gether. Greatly delayed growth of the lower jaw seems to be the root of the problem since another grantee study indicates that the jaws of such children will, by age ten, usually grow enough to im-prove chewing and appearance. Therefore, facial surgery for these patients is not always desirable, but palatal surgery is usually necessary because jaw growth comes too late to help the divided palate.

Environment and Clefts

A number of birth defects, including clefts, are more common in the generally unfavorable environments associated with ignorance and poverty, but whether these defects are due to poor nutrition, poor care, more frequent infections or some other factors is not known. There are, however, several environmental hazards in preg-nancy more specifically related to clefting.

In one study completed under an Institute grant, French investigators recently reported that immunological insult will produce clefts in rats. Their findings showed that a single dose of serum from rabbits sensitized by previous injections of rat kidney, will, if injected between the seventh and eleventh days of pregnancy, result in a high percentage of rat offspring with cleft palates and damaged nervous systems.

Mice also can be induced to produce cleft offspring when given a single injection of the adrenal hormone, cortisone, on the twelfth day of pregnancy. Unfortunately, however, the effects of hormones on embryos are imperfectly understood at present.

Other chemicals also affect the development of the palate in various ways. For example, when Institute scientists compared the clefts produced in rats by the antihistamine, chlorcyclizine (and related compounds) with those caused by taking too much vitamin A, they found that the malformations were quite different. Both sides of the palate formed but failed to rotate and grow together when chlorcyclizine was administered to the mothers, whereas jaw bones fused abnormally, but palatal parts never developed properly in the case of the vitamin. Obviously different growth processes were affected by the two drugs.

It is likely that other chemicals, and perhaps even some diseases, reacting at crucial times in pregnancy may lead to clefts by interfering with embryological development.

Surgical Repair of Clefts

The problems of repair naturally vary with the individual defect. However, the most serious question invariably is how to supplement or extend deficient tissue, while retaining as much mobility as possible, minimizing scars, and avoiding interference with growth. Perhaps the surgeon's greatest challenge is the need to provide immediate function which will continue in later years after growth has changed the relative dimensions of the nose and throat. The University of Illinois and the National Institute of Dental Research have cooperated in longitudinal growth studies which show that some children, whether or not they have had their clefts repaired, talk quite well until their upper jaws and palates reach a certain stage of growth. Between age five and seven years there is a growth spurt, and, thereafter, their slightly short and less mobile palates may become inadequate to bridge the larger distance to the back of the throat and so to make certain sounds.

The Institute also is supporting a number of efforts to improve surgical techniques and to predict which will be best for a given case. To the question, "How soon should surgery be done?", there is no one answer. An analysis of nearly 600 operations made over a 15 year period at the University of Pittsburgh, showed that about 15 percent of the most seriously premature and afflicted cleft infants die in the first few weeks of life. For the survivors, a weight of at least 10 pounds, a hemoglobin of at least 10 gm. and a white blood count of above 10,000 cells per cubic mm. are prerequisites for surgical success. When surgeons waived any of these requirements before surgery, even for apparently thriving infants, complications were five times as frequent. If these standards are followed, many operations can take place at about three months of

age when such babies usually reach this weight. However, it is better in selected cases to operate later. Also when other congenital abnormalities occur, as they do in about 12 percent of the cases, the necessity for other operations must be taken into account.

Each decision must be made on an individual basis. For example, several children seen at the Institute have had submucous clefts plus more serious tongue and mouth malformations, yet they managed to compensate for these deficiencies when neurological control of the speech apparatus was adequate. It would seem then that if a child with a submucous cleft can manage to eat and speak acceptably, surgery is not indicated.

In addition to the previously mentioned findings in the University of Pittsburgh study, it was shown that improvements in anesthesia sharply reduced post-operative deaths and complications. For example, the percentage of complications for the 15-year-period was 13.4, but in the last five years it was only 5.6 with no deaths. Much of this improvement is attributable to such surgical techniques as keeping the airway open with a tube and using drugs to reduce bleeding. Nevertheless, surgeons still need to know more exactly how much blood an infant has and how much loss it can tolerate. Under Institute support, a method of measuring the actual volume of blood in a child has been developed which should be helpful in selected cases. Radioactive albumin is injected into a vein, and five minutes later a small sample of blood is withdrawn from another vein and tested for radioactivity in a measuring device. The investigators claim 95 percent reliability for this method, which is a better result than that given by the usual hematocrit estimations, derived by finding the volume of red cells in a sample of blood spun in a centrifuge. With this technique it should now be possible for a surgeon to replace the exact amount of blood lost during an operation, and so avoid under or over transfusion. It should also be noted that since the amount of radiation is 500 times less than that required for a chest X-ray, the procedure should be quite safe.

In addition to determining the best time to operate and the most promising techniques to use, considerable research is being supported to predict which patients will need a second operation and which can do without. Since the first operation in infancy is designed to make eating and breathing easier, the need for further surgery later on nearly always depends on the need to improve speech. Therefore, a decision must be made whether a particular operation is likely to help a particular child. The alternatives include relying upon an appliance called a speech bulb (or obturator) or undertaking speech training.

There is evidence from workers at the University of Iowa that the mobility of the soft palate and the side walls of the throat generally predicts the success of the so-called pharyngeal-flap operation. Patients who can move the walls toward the mid-line

and the palate toward the back of the throat are good candidates, whereas immobile throats are less likely to benefit. Fortunately, pharyngeal-flap operations do improve speech in about 90 percent of the cases where they are used.

However, where there is a mobile throat and a rather narrow gap between the nose and throat, the flap operation sometimes can be avoided and closure accomplished by injecting teflon dispersed in glycerine. The surgeon determines how much teflon to use by studying X-ray motion pictures of the throat while the patient makes certain sounds. Sometimes a second injection may be required to close the gap. Observations, to date, show that the teflon remains in position and is well tolerated.

Another way of testing speech potentials and problems requires an analogue computer for instantaneous calculation of the size of the opening based on simultaneous determinations of air flow and pressure through the nose and mouth. It has generally been assumed that measuring the escape of air through the nose is the best way to identify and separate patients who can close the gap between nose and mouth from those who cannot. It has also been assumed that the latter would need surgery or appliances. Now it is known that this test works well only when the size of the gap is no more than two-tenths of a square centimeter. When the opening is larger, the test becomes less reliable since it does not reveal the effects of less forceful exhaling or blockage in the nose.

Speech Research

Speech is difficult to assess objectively because evaluation depends upon the hearer as well as upon the speaker. It is significant, therefore, that a "voice systems nasality meter" has been devised to make reproducible and objective analyses of normal and abnormal speech. The investigators responsible for this development report that electric recording of selected words shows that normal people have a wide range of nasal as well as pure sounds, above 20 units on this system, whereas very defective speech ranges below 10 units, and some impairment exists between these ranges.

Investigators in Rochester, New York, have developed instruments to compare the rate and volume of airflow through the nose and mouth during speech of normal and cleft subjects of various ages. This work is also helping to establish some of the physical bases of speech and to determine limits of variation beyond which lies abnormal speech.

Those who try to assess speech need ways to visualize and record in three dimensions what happens as parts of the mouth and throat work together. When lack of symmetry between right and left sides is a factor in faulty speaking, chewing, or swallowing, it is especially important to be able to distinguish relative motion in

depth without disturbing these processes. X-ray motion pictures are helpful, but interpretation of three-dimensional action on flat film or television screen is difficult. Stereoscopy requires two cameras, two tubes, special goggles and other equipment to produce binocular effects. Now, however, Duke University investigators have devised a cinefluorographic unit which uses monocular vision to separate moving objects.

When pictures are taken as fast as 64 frames a second while the X-ray machine revolves around the subject at a fixed distance, an illusion of objects moving in opposite directions is produced. This optical effect gives a perception of depth sufficient to distinguish the motion of structures on each side of the throat. It is then possible to observe whether a speech appliance is closing one side of the throat but allowing air to escape on the other.

Appliances, called obturators, for closing the gaps caused by clefts may be very helpful as temporary aids to simplify infant feeding. By keeping the tongue out of the cleft and stimulating the blood supply, such appliances may at that stage encourage narrowing of the cleft. Since the devices are individually fitted and easily adaptable to changes in growth, they are particularly helpful during the period that must sometimes elapse before surgery. Also, they are important in improving the shape of the jaws and the position of teeth, which is often faulty in cleft children. Sometimes, too, artificial teeth are fastened to obturators when natural ones are missing, and the appliances are worn like dentures.

It is wise to reassess the value of appliances in relation to speech requirements. In general, appliances may decrease the nasal quality of cleft palate speech and improve its intelligibility. Those patients who benefit least from their use generally have longer but less mobile soft palates, tongues in a lower position, and less full upper lips. When palates are short, appliances are most successful for improving speech and interfere least with swallowing.

The effects of various appliances on air flow and volume in relation to specific speech sounds also have been studied with special instruments. This information has been coordinated with cephalometric tracings of lip and tongue positions to determine the most effective obturator design.

How completely appliances should cover the gap left by a cleft is another important consideration in their use. It sometimes happens that, as children's muscles develop, they are able to block the opening and dispense with obturators entirely. Therefore, a group of scientists made a study to see whether a near-fit in an appliance might stimulate speech muscles to develop further without seriously impairing speech. These investigators at the University of Kansas conclude that complete closure is more important for young children learning to speak than it is for maintaining good articulation in somewhat older patients. They considered that heavy or

overlapping appliances in older children may hinder the development of the muscle coordination needed to outgrow dependence on the appliance. However, for those who can never close the gap, there is a limit beyond which a smaller speech bulb will only reduce intelligibility. It sometimes becomes necessary to reduce the size of an appliance several times over a period of months before it is possible to decide whether or not it can be discarded.

Since appliances are always a nuisance and sometimes a failure, and the effects of surgery, though permanent, are not always successful, speech training might appear to be the best way to help a child communicate normally. It is true that speech therapy can help many people with clefts to talk better, but it is effective only for those whose physical limitations are not too great, and whose emotional and psychological makeup is suitable. Therefore, it is important to test children carefully to make sure that they will be able to benefit from such a time-consuming and expensive effort, and that surgery, appliances, or both, have previously been tailored as successfully as possible to meet their individual needs. Failure in speech training is especially disheartening.

Occasionally a child is discovered who appears to be anatomically and emotionally suitable for speech therapy, does not have a cleft, but proves to lack certain nerves. Being unable to feel with the tongue and throat walls, such patients have difficulty chewing, swallowing, and talking. It is almost impossible to teach those who lack sensation and perception to speak clearly. The Institute is conducting and supporting studies of the way the mouth feels and reacts to sensation. The information thus acquired should help patients with a variety of oral-facial problems.

Psycho-social Research in Clefting

Cleft palate investigators are also concerned about personal reactions of the patient to his condition. A review of the literature on this subject accumulated over the past 25 years indicates that, whereas many cleft people are highly intelligent, the average intelligence of the group consistently runs slightly lower than that of the rest of the population. Since the kinds of clefts differ, scientists are beginning to think that people with clefts should not be considered as "a population," but should be further subdivided to make statistics truly meaningful. The intelligence findings, for example, may be affected by the higher percentages of other defects which cleft people in general have, or by the fact that many measures of intelligence are tied in with word facility.

Two studies of children 10 and 11 years old show that whether they are cleft, otherwise handicapped, or normal, they all would prefer crippling with immobility to facial disfigurement. Since appearances are important, especially to adolescents, maintenance of teeth in good condition and use of orthodontic procedures suitable to each stage of growth are especially desirable to support the morale of cleft palate patients.

Speech scientists are aware that generalities are misleading in studies of behavior and emotional health among clefted people. They note that children with severe speech problems tend to have lower intelligence and more troublesome behavior than those with better speech patterns, but they do not know which is cause and which is effect. They also report that children may recognize words well, but be slow to use them in expressing themselves. Cleft youngsters, they find, tend to be less creative, more passive, and to use fewer gestures than others in their age groups. The question has been raised whether the cause may at times be slight brain damage or whether other difficulties in communication are largely responsible. For example, missing or badly positioned teeth may make speech troublesome and interfere with communication. Communications difficulties may stem from loss of hearing.

It is well established that deafness may result from infections, and that these are more likely to reach the ear when the palate is open. Formerly, about 50 percent of cleft children were more or less deaf. Fortunately, antibiotics and improved care are reducing this hazard.

Promising Avenues of Research

The Dental Institute has supported workshops to collect information and encourage diversified research on the embryonic development of normal and cleft palates. Other meetings held under Institute auspices have encouraged cooperation and coordinated training of dental and speech scientists. Unfortunately it is not always possible for a youngster, who has had adequate pediatric care and surgical repair, to find in his community the help he needs later in order to speak acceptably. To improve this situation, the Institute supports a number of cleft palate centers where the problems of cleft children and their families can be considered and the patients treated as a whole and on a continuing basis. The findings of studies made in these centers should, in time, improve cleft palate therapy everywhere.

TOOTH TRANSPLANTS

Mr. FLOOD. Speaking of the Japanese, what about their experiments with monkeys and transplanting teeth? Have you been reading about that lately?

Dr. KRESHOVER. Yes, sir. This is an area of continuing interest in the field of dentistry, as you certainly imply. We are faced, on the other hand, with the same kind of difficulties, not as dramatic perhaps as in transplantation of other organs, tissues, or parts; namely, the so-called immunological reaction, the rejection phenomenon, the inability of the recipient host to accept the transplant. And this obtains with the tooth as well as it does with other organ structures of the body.

We find, for example, that a so-called autogenous transplant, which is a transplant of a tooth from one location in the same individual to another one, is one that would be rather well received.

On the other hand, the so-called homogeneous transplant from one man to another man, within the same species, is not as favorably received.

Mr. FLOOD. Transplantation has become dramatized very much recently because of the heart.

Dr. KRESHOVER. Yes, sir.

I would say our approach, Mr. Flood, has been one that is rather unique because we have elected to go in the direction of synthetically prepared artificial or acrylic-like materials which, as you know, are nonsensitizing, they are nonabsorbable, they can be reproduced esthetically and they can be readily fabricated.

You recall last year you had a reasonably similar question that called attention to our efforts in this regard with experimental studies in the baboon where replications of teeth implanted in the mouth are standing up very well indeed.

Mr. FLOOD. Mr. Natcher?

Mr. NATCHER. No questions, Mr. Chairman.

Mr. FLOOD. Mr. Casey?

DENTAL RESEARCH INSTITUTES

Mr. CASEY. On page 94, Doctor, of the backup book here, the justifications, you make mention that there are six dental research institutes authorized and two have been estabilshed at the University of Pennsylvania and the University of Washington, and you state four other centers are in the planning stage.

Dr. KRESHOVER. I am sorry, Mr. Casey, my 94 does not read the same way yours does.

Mr. CARDWELL. It is possible the page numbers are different, sir.

Dr. KRESHOVER. Yes, sir; I was looking at the wrong place.

Mr. CASEY. On the left-hand side, item 2, you state that there are four other centers in the planning stage.

Dr. KRESHOVER. Yes, sir.

Mr. CASEY. But elsewhere you just state there are five in various stages. What is the sixth one you have reference to?

Dr. KRESHOVER. The item on the left side of the page, Mr. Casey, was in testimony before this subcommittee a year ago and represented our development as of that date; as of today, the number of institutes has

increased from the two to five, which means of course that some of the ones that were in the planning stage a year ago represented plans to submit proposals. Perhaps the use of the word "planning" is ill-advised, because it might have connoted their already having been estabilshed and in an early stage of development. But they actually were planning to submit proposals at that time.

Mr. CASEY. When they submit a proposal, it goes directly to you, I presume?

Dr. KRESHOVER. Yes, sir.

REVIEW SYSTEM FOR APPLICATIONS

Mr. CASEY. And then you in turn, if you think it is meritorious, do you then submit it to the advisory council?

Dr. KRESHOVER. It goes through a dual review system. We have established within the National Institute of Dental Research an advisory committee on dental research institutes and special programs. This constitutes the primary review.

The primary review then provides the information with an appropriate recommendation that will then go to the National Advisory Dental Research Council for its recommendation. This then in turn will go to the Surgeon General for his endorsement.

Mr. CASEY. This advisory council meets how often?

Dr. KRESHOVER. Three times a year.

Mr. CASEY. When is its next meeting?

Dr. KRESHOVER. The next regularly scheduled meeting will be approximately June 13. They are customarily 3-day meetings.

Mr. CASEY. I do not know as I completely followed you, but the Advisory Council, do they look at it first or do you look at it or do you look at it together, or at separate times or what?

Dr. KRESHOVER. The proposal is submitted as a formal application. The formal application is then reviewed by the Dental Research Institute's Advisory Committee on Dental Research Institutes and Special Programs. This is the group that will site-visit the university, examine the program from the standpoint of its scientific merit, as well as other components that would establish its merits. Then, with an appropriate recommendation, it will go to the advisory council, which is the legislatively established advisory body for the categorical institutes. Council will then make the official recommendation.

Mr. CASEY. One is an advisory council and the other is what, an advisory committee?

Dr. KRESHOVER. Yes, sir.

Mr. CASEY. The committee is in-house?

Dr. KRESHOVER. No, sir. It is constituted of consultants, experts in a variety of science fields from the outside community of science. Most of these are university people.

Mr. CASEY. Is not your council outside people too?

Dr. KRESHOVER. Yes, sir; it is.

Mr. CASEY. You have a dual review then?

Dr. KRESHOVER. Yes, sir.

The first committee is constituted of people expert in the professional field. The advisory council, on the other hand, has membership

established by legislative act. And Dr. Shannon might wish to expand on the composition of the council.

Dr. SHANNON. I think I can clarify it a little.

### UNIVERSITY OF TEXAS DENTAL SCHOOL APPLICATION

Mr. CASEY. Let me tell you what my problem is and then you can tell me what chances I have now.

The University of Texas Dental School, as you probably know, submitted last year an application to establish a research center.

Dr. KRESHOVER. They did, yes, sir.

Mr. CASEY. They were visited, as I understand, on the site. They had two applications, one for matching funds, for facilities, construction, and then one to initiate the research center as to its operating funds.

Dr. KRESHOVER. Yes, sir.

Mr. CASEY. They had a visit by the site committee, as I understand, and the visiting site committee approved, so I understand—I have only heard one side of it so far—and the application for construction funds was approved subject to their getting the operating funds. Then you turn around and their operating funds were turned down. Is this two different committees?

Dr. KRESHOVER. Yes, sir. The parallel is actually no different than the procedural mechanisms for any requests for grant support. It goes through a primary review. The primary review looks at certain parameters, limited I must say to the consideration of scientific content. On the other hand, there are a number of other considerations that come into an evaluation of a grant application or a training grant application or a dental research institute application.

These broader issues take into consideration the long-range promise, the national purpose, and a wide variety of components related to university relationships. The preliminary review does not necessarily include all of these. The preliminary review is one of several factors considered by the council. It will look at a variety of components.

### SELECTION OF ADVISORY COUNCILS

Mr. CASEY. How are these advisory councils selected?

Dr. KRESHOVER. May I defer to Dr. Shannon?

Mr. CASEY. Yes.

Dr. SHANNON. In the first place, the advisory councils are not appointed by us. Heretofore they have been appointed by the Surgeon General. At the present time I believe the authority resides in the Secretary's Office.

We make proposals for membership with a view to having a distribution of the various skills that are necessary, together with some lay members to provide some representation, or some reflection, of broad public interest as distinct from technical considerations. These nominations go to the Office of the Secretary, which may, at times, substitute members who, they feel, are more suited, viewing the program from their level. Then these appointments are made.

Since this body must recommend all grants before they can be paid, they have a great influence on the distribution, especially in organizing research institutes. This determination is made on the basis of

the dollars available and the quality of applications they have to act on.

They will exercise their views over such things as geographic distribution. When we are establishing research centers, where one of the purposes is to broaden the geographic distribution, were we not to take that into account, it would be the responsibility of the Council to do it. And I might say that they see all aspects of the dental program, training, research, direct operation, and the like.

Now the Technical Review Committee, on the other hand, is composed of people that are nearer to the subject of science. This one review group will review all of the Dental Research Institute applications. In this way they will arrive at a comparative assessment of the worth of each one in relation to the others.

There is continuity in these groups—they serve for a period of 4 or 5 years—so they will see not only the applications that are before them this year but they will have had the experience of what they saw in previous years. This is basically a technical review group to assure that the resources are adequate, the science backup is adeqaute, and that it is embedded in an area of science where it will flourish.

This is a straightforward technical decision on their part. At times, the technical decision will be overridden by the Council because of the other inputs at their level.

I do not know the reason and I am surprised to hear that the Research Facilities Construction Council said that funds would be made available and that the program people would not approve the program. Usually it is the other way around because of the shortage of construction funds.

REPORT ON UNIVERSITY OF TEXAS APPLICATION

In this case I would like to ask Dr. Kreshover to give you a report on precisely what happened here.

Mr. CASEY. I would be glad to have it.

(Information requested follows:)

The following information is submitted on the application review process for Dental Research Institute grants, with specific reference to the application made by the University of Texas:

Such grant applications follow the general NIH pattern of dual review by external advisory bodies. They are first received by the Division of Research Grants and assigned to the National Institute of Dental Research. Institute staff then reviews the applications to assure that they are complete and ready for appraisal and action by the Advisory Committee for Dental Research Institutes and Special Programs. Composed entirely of persons outside of the Department, including university administrators, educators, and scientists, this group is responsible for the primary review in the dual process.

As part of this review, the Advisory Committee, augmented as necessary by ad hoc members with other scientific backgrounds, makes a site visit to the applicant institution. At that time, it examines all factors bearing on the basic concepts and scientific merit of the application. The Advisory Committee then prepares a critique of the application and recommends approval or disapproval to the National Advisory Dental Research Council.

As the final external review body, the council considers the application, together with the advisory committee's recomendations, and makes its own recommendation for approval or disapproval on the basis of the proposal's adherence to the principles established for the organization and administration of the Dental Research Institute program, demonstration of outstanding scientific leadership and accomplishments, geographic distribution, and commitment of total university resources.

Applications disapproved by the National Advisory Dental Research Council cannot, under law, be funded by the Secretary of Health, Education, and Welfare. Those approved by the Council can be funded within the limits of appropriations available to the Secretary.

Following this process, the Advisory Committee recommended approval by the Council of the application for a Dental Research Institute grant made by the University of Texas. The application was reviewed by the Council at its November 1967 meeting and disapproved because in its judgment the proposed institute did not fully meet the prescribed standards.

Subsequently, the university submitted a second application. The Advisory Committee has made a second site visit and will present its critique and recommendations to the Council at its next meeting scheduled for June 13–15, 1968.

Because of the juxtaposition of an application for an institute grant and an application for research facilities at the University of Texas, it is important to clarify their relationship. Denial of the institute grant was not influenced by the status of the facilities application, since adequate facilities are currently available for the initial stages of institute program development. On the other hand, the facilities grant logically had to be tied to the award of an operating grant. It is possible that the confusion on this point arose from the fact that the facilities application was reviewed in June 1967, and the operating grant application was reviewed in November 1967.

Dr. SHANNON. The dual review system is necessary because the councils, by their very makeup and by the mass of work they have to do, cannot arrive at mature technical judgments on specific things. Having an appraisal from a technical group that is competent, they can make comparative judgments and look at the array of programs primarily from the standpoint of broad general policies and from the standpoint of program emphasis and things of that sort.

Mr. CASEY. Up until a few years ago, none of the scientific community who were employed by any of the State of Texas institutions were appointed to any of your advisory councils because of the belief that there was a constitutional prohibition. I think we finally had an attorney general's opinion and I do not know whether you accepted that, but now the constitution has been amended.

Are you aware of that now?

Dr. KRESHOVER. I might say, Mr. Casey, even prior to this time there was a member of the National Advisory Dental Research Council from your State of Texas. Dr. Lawrence Haskew served on our Council for a period of 4 years and retired after meritorious service a year ago.

Mr. CASEY. Thank you.

And thank you, Mr. Chairman.

JUSTIFICATION MATERIAL

Public Health Service

National Institute of Dental Research

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $30,307,000 | $30,414,000 |
| Transfer to "Operating Expenses, Public Buildings Service", General Services Administration | -19,000 | ..... |
| Total | 30,288,000 | 30,414,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 97 | Research | | $15,617,000 | | $15,626,000 | | +$9,000 |
| | General research support grants | | (1,256,000) | | (1,194,000) | | (-62,000) |
| | Scientific evaluation grants | | (42,000) | | (42,000) | | (.....) |
| | Categorical clinical research centers | | (400,000) | | (400,000) | | (.....) |
| | Dental research institutes | | (3,000,000) | | (3,000,000) | | (.....) |
| 103 | Fellowships | | 1,971,000 | | 2,015,000 | | +44,000 |
| 104 | Training | | 5,469,000 | | 5,609,000 | | +140,000 |
| | Direct operations: | | | | | | |
| 105 | Laboratory and clinical research | 231 | 4,541,000 | 236 | 4,740,000 | +5 | +199,000 |
| 110 | Collaborative research and development | 4 | 841,000 | 4 | 844,000 | .. | +3,000 |
| 111 | Biometry, epidemiology and field studies | 22 | 432,000 | 22 | 435,000 | .. | +3,000 |
| 112 | Review and approval of grants | 39 | 647,000 | 40 | 706,000 | +1 | +59,000 |
| 113 | Program direction | 26 | 403,000 | 27 | 439,000 | +1 | +36,000 |
| | Total obligations | 322 | 29,921,000 | 329 | 30,414,000 | +7 | +493,000 |
| | Unobligated balance, reserve | 10 | 367,000 | ... | ..... | -10 | -367,000 |
| | Total obligations and reserve | 332 | 30,288,000 | 329 | 30,414,000 | -3 | +126,000 |

Obligation by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 322 | 329 | +7 |
| Full-time equivalent of all other positions. | 5 | 5 | .. |
| Average number of all employees..... | 308 | 315 | +7 |
| Personnel compensation: | | | |
| Permanent positions..... | $2,903,000 | $3,007,100 | +$104,100 |
| Positions other than permanent..... | 30,000 | 30,000 | ..... |
| Other personnel compensation..... | 32,000 | 32,000 | ..... |
| Total personnel compensation..... | 2,965,000 | 3,069,100 | +104,100 |
| Personnel benefits..... | 337,000 | 347,100 | +10,100 |
| Travel and transportation of persons..... | 130,000 | 147,800 | +17,800 |
| Transportation of things..... | 30,000 | 36,000 | +6,000 |
| Rent, communications & utilities..... | 97,000 | 101,000 | +4,000 |
| Printing and reproduction..... | 35,000 | 35,000 | ..... |
| Other services..... | 312,000 | 338,000 | +26,000 |
| Project contracts..... | 629,000 | 629,000 | ..... |
| Services of other agencies..... | 200,000 | 200,000 | ..... |
| Payment to "National Institutes of Health management fund"..... | 1,534,000 | 1,601,000 | +67,000 |
| Supplies and materials..... | 370,000 | 394,000 | +24,000 |
| Equipment..... | 230,000 | 271,000 | +41,000 |
| Grant, subsidies & contributions..... | 23,057,000 | 23,250,000 | +193,000 |
| Subtotal..... | 29,926,000 | 30,419,000 | +493,000 |
| Deduct quarters and subsistence charges.... | 5,000 | 5,000 | ..... |
| Total obligations by object..... | 29,921,000 | 30,414,000 | +493,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $30,307,000 |
| Transferred to "Operating expenses, Public Buildings Services," General Services Administration | -19,000 |
| Unobligated balance, reserve | -367,000 |
| 1968 total estimated obligations | 29,921,000 |
| 1969 estimated obligations | 30,414,000 |
| Total change | +493,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of 1968 pay increases | ... | ..... | ... | $42,000 |
| 2. One extra day of pay in 1969 | ... | ..... | ... | 11,000 |
| Total built-in increases | ... | ..... | ... | 53,000 |
| B. Program | | | | |
| 1. Research grants | ... | $15,617,000 | ... | 9,000 |
| 2. Fellowships | ... | 1,971,000 | ... | 44,000 |
| 3. Training grants | ... | 5,469,000 | ... | 140,000 |
| 4. Laboratory and clinical research | 231 | 3,370,000 | 5 | 125,000 |
| 5. Review and approval of grants | 39 | 444,000 | 1 | 35,000 |
| 6. Program direction | 26 | 282,000 | 1 | 20,000 |
| Total program increases | ... | ..... | 7 | 373,000 |

| Increases--continued | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| Payment to "National Institutes of Health management fund" for centrally furnished services: | | | | |
| Laboratory and clinical research | ... | 1,171,000 | ... | 33,000 |
| Collaborative research and development | ... | 6,000 | ... | 2,000 |
| Review and approval of grants | ... | 203,000 | ... | 19,000 |
| Program direction | ... | 121,000 | ... | 13,000 |
| Total management fund increases | ... | ..... | ... | 67,000 |
| Total increases | ... | ..... | 7 | 493,000 |
| Total net change requested | ... | ..... | +7 | +493,000 |

Explanation of Changes

Research grants--The net increase of $9,000 represents an increase of $934,000 for competing requirements of the regular program. This is offset by a decrease of -$863,000 in noncompeting continuations, and a decrease of -$62,000 in the general research support grant program.

Fellowships--The increase of $44,000 will provide funds for increased stipends for postdoctoral awards.

Training--The increase of $140,000 will provide funds for increased stipends for postdoctoral awards.

Laboratory and clinical research--The increase of $125,000 and 5 positions will allow for expansion of research in dental caries and oral and related diseases.

Review and approval of grants--The increase of $35,000 will provide support for one additional position necessary in the management of the extramural programs.

Program direction--The increase of $20,000 will support one additional position in the Office of the Director in the area of program analysis and review.

## Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301--Research and Investigation, in general | Indefinite |
| Title IV, Part C--National Institute of Dental Research | Indefinite |

### PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume V.

The Public Health Service Act, Title IV, National Research Institutes, Part C, National Institute of Dental Research--

"Sec. 421. There is hereby established in the Public Health Service a National Institute of Dental Research (hereafter in this part referred to as the 'Institute').

"Sec. 422. In carrying out the purposes of section 301 with respect to dental diseases and conditions the Surgeon General, through the Institute and in cooperation with the National Advisory Dental Research Council (hereafter in this part referred to as the 'Council'), shall--

(a) conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of dental diseases and conditions;

.....

(c) provide fellowships in the Institute from funds appropriated or donated for the purpose;

.....

(f) provide training and instruction and establish and maintain traineeships, in the Institute and elsewhere in matters relating to the diagnosis, prevention, and treatment of dental diseases

and conditions with such stipends and allowances (including travel and subsistence expenses) for trainees as he may deem necessary, the number of persons receiving such training and instruction, and the number of persons holding such traineeships, to be fixed by the Council, and, in addition, provide for such training, instruction and traineeships through grants, upon recommendation of the Council, to public and other nonprofit institutions."

Explanation of Transfers

| | 1968 Estimate | Purpose |
|---|---|---|
| Transferred to: | | |
| "Operating expenses, Public Building Service", General Services Administration..... | -$19,000 | Transfer of rental costs to GSA |

Justification

National Institute of Dental Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 322 | $3,302,000 | 329 | $3,416,200 | +7 | +$114,200 |
| Other expenses | ... | 26,619,000 | ... | 26,997,800 | .. | +378,800 |
| Total | 322 | 29,921,000 | 329 | 30,414,000 | +7 | +493,000 |

General Statement

The National Institute of Dental Research conducts and supports basic, clinical, and applied research and research training, in the causes, diagnosis, prevention, and cure of oral diseases and disorders: (1) conducts intramural laboratory, clinical and field research, (2) supports dental and medically-related research and research training by assisting individuals, universities, institutions, and agencies through grants-in-aid for research projects, training, fellowships, and dental research institutes, (3) conducts and supports collaborative and developmental research programs aimed at specific dental problems where major advance seems clearly possible, and (4) disseminates and supports dissemination of research findings and related information. The long-range objective of the Institute is the improvement in the oral health of all individuals through the greater understanding of the biological phenomena underlying oral diseases and disorders, the advancement of capability for the diagnosis, treatment, and prevention of oral disease, and the acceleration of the effective flow of new knowledge to health practice.

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Research projects..... | $10,919,000 | $10,990,000 | +$71,000 |
| Special programs..... | 4,698,000 | 4,636,000 | - 62,000 |
| Total research grants..... | 15,617,000 | 15,626,000 | +9,000 |

Program plans for 1968 and 1969

Dental Caries and Hard Tissues Program

Dental caries is a multifactorial disease resulting from the interaction of three different categories of contributory factors: host resistance, dietary substrate, and oral microflora. Accordingly, a concerted effort will be continued to (1) acquire additional definitive information on agents such as fluoride which enhance the resistance of the tooth to destructive acid attack, (2) investigate the chemotherapeutic elimination or control of the noxious microorganisms involved, and (3) seek ways of reducing the fermentable, acid producing ingredients of the diet.

Since the effectiveness of fluoride in preventing dental decay is seemingly largely dependent upon the fluoride content of the enamel, studies of factors affecting enamel uptake of fluoride will continue to be emphasized. Of fundamental importance to this research are additional investigations of the precise crystal structure of dental hard tissues, including the process by which they become mineralized and their chemical interaction with the body fluids. The investigation of the role of trace elements other than fluoride in the resistance of the tooth to dental caries also will be encouraged.

The observation that the organisms responsible for the initiation of dental decay are streptococci requires further study of their metabolic behavior in both man and lower forms of mammalian life. Thus, investigators are seeking to compare the relative ability of certain microorganisms to produce acid from a variety of carbohydrates commonly found in the diet. Other research has as its objective clarification of the growth requirements and immunologic specificities of these microorganisms, and the chemical pathways involved in the development of caries. Studies of the distribution of potentially cariogenic streptococci in human populations varying widely in susceptibility to dental caries will be continued.

Since the microorganisms implicated in dental caries have been found to produce highly adherent bacteria-rich films on tooth surfaces (plaque) which are considered a prerequisite for the development of the disease,

efforts will be intensified to investigate further the chemical nature of this material and the factors which affect its deposition. The recent observation in animals that the plaque-like substances which adhere to the crown of the tooth can be dissolved by the enzyme dextranase suggests a possible means of preventing dental decay in man through its administration. Studies of the use of antibiotics in the control of decay-producing micro-organisms will be supported in human population groups, as will be an evaluation of the effect of substituting in the diet sugar thought to be less conducive to dental decay.

Periodontal Diseases and Soft Tissues Program

Periodontal diseases include a number of conditions affecting the investing tissues of the dentition. Since greater knowledge of the normal structure and function of these components is critical to the better understanding of periodontal diseases and their ultimate prevention, basic science studies of the normal bone, connective tissues and epithelial covering of the oral cavity will be continued during 1968 and 1969.

Periodontal diseases are commonly characterized by a loss of the epithelial attachment to the tooth with a concurrent or ensuing degradation and resorption of the connective tissue and bone supporting the tooth. Studies of gingival wound healing and the prevention and inhibition of bone resorption will be encouraged. Emphasis will be placed on histo-pathological and biochemical studies to clarify the relationship between gingival inflammation and alveolar bone resorption.

Recent developments of animal model and tissue culture systems for the investigation of periodontal diseases have permitted the identification of a number of potential physical, physiological and psychological factors in the etiology of periodontal diseases. Studies designed to evaluate the interactions of these factors, as well as to identify additional contributing conditions, are being supported. Other research into the status of host tissues and the natural resistance of these tissues to periodontal diseases is also being encouraged.

In order to accelerate clinical research in periodontal diseases, an accurate and reproducible measurement technique must be developed for the assessment of clinical changes occurring in periodontal tissues during disease and therapy. Thus, research will focus on the development of direct, radiographic, and photographic measurement techniques.

Oral and Dental Infection and Conditions

The most common oral soft tissue lesions are herpes simplex (fever blisters and cold sores) and aphthous stomatitis (canker sores). The clinical histories of these conditions show a common pattern of frequent recurrence at irregular intervals following an initial attack, usually in childhood. The recurrence of the herpetic lesions can usually be

correlated with a lowering of host resistance through systemic or local stress situations, i.e., fever, sunburn, and trauma.

Investigations designed to define better the pathogenesis of these oral lesions will be carried out, and special emphasis given to study at the cellular level of the triggering mechanism which results in their recurrence. Development of improved diagnostic techniques and therapeutic measures for these diseases will also be encouraged.

Oral Neoplasia

Approximately six percent of all malignancies diagnosed occur in the oral cavity. Current therapeutic techniques, primarily surgical and radiation procedures, result in substantial morbidity and residual disfigurement of patients. Obviously, research into early detection and improved diagnostic techniques for oral cancer is needed, as is an exploration of chemotherapeutic agents and other approaches that can control the disease without causing tissue destruction and facial disfigurement.

Salivary Gland Physiology

The salivary gland system produces and secretes the liquid environment of the oral apparatus. Recent studies have established that salivary secretions play a role in most diseases of the teeth and supporting structures. Directing attention particularly to the pathogenesis of dental caries and the periodontal diseases, current studies will be carried out to (1) further define the role of the organic and inorganic constituents of saliva in disease initiation and progression, and (2) determine the metabolism of proteins by salivary glands.

Normal and Abnormal Growth and Development Including Congenital (Genetic) and Acquired Diseases and Anomalies.

The evaluation and refinement of surgical and rehabilitative treatment for the cleft palate child is to be continued. Studies will embrace (1) the identification of diagnostic procedures for determining the anatomical and physiological adequacy of the oral structure for speech; (2) the better understanding of sensory and motor mechanisms in the pharyngeal, laryngeal, and oral area; (3) the development of standard measures of the degree of speech competency; (4) the approaches to better restoration of masticatory and overall neurological function; and (5) the attainment of optimum dental and facial growth. Studies of psychosocial factors which affect the adjustment of the cleft palate individual and his family to society will be continued as corollaries to these studies.

Studies of the causes of the cleft syndromes to clarify genetic and other developmental factors are to be emphasized. In investigations of teratogenic agents responsible for oral-facial malformations.

emphasis will be placed on the mode of action using biochemical methods. Particular attention will be paid to interspecies variability including selected sub-human primates and the pharmacological distribution and metabolism of specific agents which produce cleft palate and other oral-facial malformations. It is anticipated that two new centers for multi-disciplinary studies into the etiology of clefts will be started by 1969.

The development of interceptive and corrective treatment procedures for malocclusion will be continued. Epidemiologic studies will be encouraged to develop criteria for assessing the prevalence and severity of the occlusal anomalies in populations. These criteria should aid in detecting the need for preventive orthodontic care at an early age.

Anthropological and other related studies are needed to provide information concerning the normal growth and development patterns of the oral-facial region. Such knowledge is necessary for the early diagnosis of incipient malocclusion. Proceeding from this base, clinical orthodontic research programs will be needed to develop practical techniques to prevent malocclusion and thereby reduce or perhaps eliminate the need for corrective therapy. In addition, projects aimed at evaluating prevention and interceptive procedures for the treatment of malocclusion, which are applicable to large groups of individuals, will be supported. Research will also examine tissue response (e.g. bone changes) to various mechanical and physical forces as encountered in orthodontic therapy; and longitudinal and comparative studies in the area of physical anthropology will be continued to provide the necessary correlations between dental age, chronological age, and maturity.

As part of a program of collaborative research with various treatment and rehabilitation resources, support will be given to the development of centers for storage, retrieval, analysis, and dissemination of data collected in studies of congenital and acquired anomalies.

Materials Science

Since 98 percent of the population suffers from dental caries, any significant improvement in restorative materials and techniques would have a far-reaching impact. A concerted effort will be directed to the development of an adhesive filling material that will bond chemically to the hard structures of a tooth. As part of the broad study of physical and chemical properties of synthetic and biological materials and their relations to the oral environment, bonding mechanisms and properties of various substances will be examined.

Emphasis will also be placed on the development of biologically acceptable implants to replace lost or missing teeth. Continuing studies over the past five years show that plastic implants have been uniquely successful in being maintained in the jaws of sub-human primates in the same functional capacity as are natural teeth. Clinical trials with human

subjects will be conducted as soon as the physical and toxicological properties of the plastic implants are determined.

Efforts are being made to spur progress in materials science by bringing the skills and knowledge of industry increasingly to bear on oral health problems.

The number of individuals suffering aesthetic and functional defects from radical surgery for the removal of cancerous tissue is increasing. The impressive survival rate of these persons, who now appear as 30,000 new cases each year, and the increasing number of congenital oral-facial defects in the expanding population, impose an obligation to place greater emphasis on developing prostheses (replacement parts) which are more functional and which better meet aesthetic requirements. Accordingly, studies which characterize the physical, chemical, toxicological, and aesthetic properties of materials for maxillofacial prosthesis will be carried out, and clinical evaluations will be made as new materials become available. One aspect of this research will focus on polymer degradation due to mechanical stress, chemical absorption, surface defects, and ultraviolet light exposure. Hopefully, materials and fabrication methods can be altered to eliminate or circumvent failure of restorations and to lessen their cost to the patient.

Dental Research Institutes (Centers)

The national purpose of the newly established dental research institute grant support program is to create centers of excellence in the sciences related to oral health. The program is designed to develop broad, interdisciplinary, university-based complexes serving national as well as regional purposes with adherence to high standards of scientific merit and fiscal accountability. The program seeks to attract to the dental environment and to the solution of oral health problems the knowledge and skills of personnel in disciplines not heretofore intimately involved in dental research.

The institutes will build on and extend existing institutional research strengths, provide for participation in multiple disciplines, facilitate the cooperation of a broad range of biological, physical, and social sciences in the study of problems of common interest, and interact with the educational programs of their parent universities by having appreciable components of their investigator staffs serve also as members of the academic departments that represent their basic fields of competence. The institutes will also seek out and align themselves, wherever practicable, with other existing regional resources, including educational and research institutions, hospitals, computer facilities, Medlars regional centers, and primate colonies. Such interactions will provide added strengths to other institutions within the geographic area.

Currently, five dental research institutes are in various stages of development at the following universities: Alabama, Michigan, North Carolina, Pennsylvania, and Washington. It is expected that two or possibly three more centers will be initiated in 1968 and 1969.

Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting continuations | 225 | $8,581,000 | 196 | $7,718,000 | -29 | -$863,000 |
| 2. Competing projects | 72 | 1,853,000 | 92 | 2,872,000 | +20 | +1,019,000 |
| 3. Supplementals | | 485,000 | | 400,000 | | -85,000 |
| 4. Subtotal regular program | 297 | 10,919,000 | 288 | 10,990,000 | -9 | +71,000 |
| 5. General research support | | 1,256,000 | | 1,194,000 | | -62,000 |
| 6. Scientific evaluation | | 42,000 | | 42,000 | | ..... |
| 7. Categorical clinical research centers | | 400,000 | | 400,000 | | ..... |
| 8. Dental research institutes | | 3,000,000 | | 3,000,000 | | ..... |
| 9. Total research grants | 297 | 15,617,000 | 288 | 15,626,000 | -9 | +9,000 |

Research Grants Program Analysis

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Dental caries and hard tissue studies | $3,603,000 | $3,623,000 | +$20,000 |
| Periodontal diseases and soft tissue studies | 2,705,000 | 2,725,000 | +20,000 |
| Oral neoplasia | 134,000 | 140,000 | +6,000 |
| Normal and abnormal growth and development including congenital (genetic) and acquired diseases and anomalies | 2,730,000 | 2,743,000 | +13,000 |
| Materials science | 1,747,000 | 1,759,000 | +12,000 |
| Subtotal regular program | 10,919,000 | 10,990,000 | +71,000 |
| General research support grants | 1,256,000 | 1,194,000 | -62,000 |
| Scientific evaluation and planning | 42,000 | 42,000 | ..... |
| Categorical clinical research centers | 400,000 | 400,000 | ..... |
| Dental research institutes | 3,000,000 | 3,000,000 | ..... |
| Total research grants | 15,617,000 | 15,626,000 | +9,000 |

## Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total Fellowships..... | $1,971,000 | $2,015,000 | +$44,000 |

### Program plans for 1968 and 1969

The fellowship program is designed to complement the training grant program by providing training opportunities in colleges and universities which do not have training grant support for this purpose. Thus, maximum utilization of location and disciplines is accomplished.

Special fellowships and research career development awards provide highly specialized research training at advanced levels. It is anticipated that more emphasis will be placed on the use of these awards since the number of qualified recipients is steadily increasing.

The additional funds in 1969 are required to support increased stipends for postdoctoral awards.

### Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting..... | 70 | $1,067,000 | 75 | $1,275,000 | +5 | +$208,000 |
| b. Competing..... | 8 | 142,000 | 3 | 55,000 | -5 | -87,000 |
| 2. Supplementals..... | (8) | 8,000 | (8) | 8,000 | .. | ..... |
| 3. New awards..... | 65 | 754,000 | 60 | 677,000 | -5 | -77,000 |
| 4. Total fellowships.... | 143 | 1,971,000 | 138 | 2,015,000 | -5 | +44,000 |

### Fellowships (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Predoctoral..... | 13 | $75,000 | 13 | $75,000 | .. | ..... |
| 2. Postdoctoral..... | 48 | 409,000 | 48 | 494,300 | .. | +$85,300 |
| 3. Special..... | 23 | 287,000 | 23 | 287,000 | .. | ..... |
| 4. Research career: | | | | | | |
| a. Career..... | 4 | 117,000 | 4 | 125,000 | .. | +8,000 |
| b. Development awards | 55 | 1,083,000 | 50 | 1,033,700 | -5 | -49,300 |
| 5. Total fellowships.... | 143 | 1,971,000 | 138 | 2,015,000 | -5 | +44,000 |

Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants.... | $5,469,000 | $5,609,000 | +$140,000 |

Program plans for 1968 and 1969

The continued expansion of existing dental schools and the creation of several new dental schools have intensified the search for competent dental research and teaching manpower. Current training grants must supply the greatest share of these young investigator trainees.

The additional $140,000 in 1969 will support increased stipends in postdoctoral awards.

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting... | 68 | $3,764,000 | 77 | $4,435,000 | +9 | +$671,000 |
| b. Competing..... | 25 | 1,330,000 | 19 | 999,000 | -6 | -331,000 |
| 2. Supplementals..... | (13) | 150,000 | (13) | 150,000 | .. | ..... |
| 3. New Grants..... | 4 | 200,000 | .. | ..... | -4 | -200,000 |
| 4. Scientific evaluation..... | (1) | 25,000 | (1) | 25,000 | .. | ..... |
| 5. Total training grants..... | 97 | 5,469,000 | 96 | 5,609,000 | -1 | +140,000 |

Training Grants (By Type of Program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Graduate training grants: | | | | | | |
| 1. Basic sciences..... | 76 | $4,394,000 | 75 | $4,506,000 | -1 | +$112,000 |
| 2. Clinical sciences.... | 21 | 1,050,000 | 21 | 1,078,000 | .. | +28,000 |
| 3. Scientific evaluation | (1) | 25,000 | (1) | 25,000 | .. | ..... |
| 4. Total training grants | 97 | 5,469,000 | 96 | 5,609,000 | -1 | +140,000 |

## Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 231 | $2,384,000 | 236 | $2,462,000 | +5 | +$78,000 |
| Other expenses | ... | 2,157,000 | ... | 2,278,000 | ... | +121,000 |
| Total | 231 | 4,541,000 | 236 | 4,740,000 | +5 | +199,000 |

### Introduction

The research mission and public health goal of this Institute's intramural program continue to be that of ascertainment of new and relevant information regarding the cause of a variety of oro-facial malfunctions, including those stemming from dental caries, periodontal diseases, oral cancer and from abnormal oro-facial development. Clearly, the net effect of successes in this quest would be measured ultimately in their expression as new and efficacious approaches to the alleviation of disease.

The development of each of the abnormal states listed above is most certainly attributable to multiple factors, about which all too little is presently known. As a consequence, the Institute's continuing systematic approach to these problems involves a tripartite commitment to relevant basic laboratory investigations; to clinical and applied investigations relating to the solution of specific questions which may be formulated as a consequence of progress made at the basic level; and to field studies directed either toward clinical trials of newer therapeutic or preventive concepts, which have evolved from basic and applied studies, or those directed toward further definition of the nature and distribution of oro-facial disease on an epidemiologic or geographic basis.

### Program plans for 1968 and 1969

#### Dental Caries

It will be recalled that, largely through the impetus of research from this Institute, community fluoridation of public water supplies has provided the single most effective public health approach to the reduction of dental decay. While in theory fluoridation would appear to be a most efficacious and economical approach to control of dental caries at the public health level, the reality is that only 40% of the population of this country is regularly exposed to this preventive measure. Moreover, it should be recognized that the acquisition of the fluoride

ion by tooth enamel consequent to exposure to fluoridated drinking water, though significantly increasing the intrinsic resistance of the tooth to decay, does little if anything to affect the immediate causative agents of decay, i.e., the oral microflora.

Consequently, the Institute's research efforts in dental caries continue to be focused upon the genesis of a more thorough understanding of oral bacteria, specifically, those strains of oral streptococci which appear to be integrally involved in the etiology of caries. These organisms are characterized by their ability to adhere tenaciously to the enamel surface, as a component of dental plaque; by preferential utilization of dietary sucrose for their growth and metabolism; and most significantly, by their propensity for producing large amounts of acid as a consequence of sucrose metabolism. It is the latter property, coupled with the close environmental relationship to the tooth surface, which presumably render these organisms highly cariogenic. Their cariogenicity has been amply demonstrated in animal experiments. Indeed, organisms of similar properties have not only been isolated from human mouths, but have also been shown to occur in numbers proportionate to the degree of severity of carious involvement.

Recognizing that specific organisms may be the key to the control of dental caries, this Institute's research is now being expanded in areas which will serve to define more precisely their absolute role in the caries process; to determine the efficacy of local treatment by antibiotic or by related bactericidal agents so as to eliminate these organisms; and to test alternate biological approaches aimed at altering the metabolism of the organisms so as to render them harmless. With regard to the latter approach, Institute scientists are much involved in experiments relating to the possible efficacy of specific enzymes, among them dextranase, whose chief effect would be that of preventing the adherence of streptococci to the tooth surface, thereby breaking the vicious circle of events which seems so essential to their role in the genesis of decay.

Finally, field studies continue to provide a rewarding outlet for the exploration of even more effective methods of extending the benefits of fluoride to a wide share of the population, particularly to children. Topical application of fluoride in fitted vinyl mouthpieces, undertaken in the school environment with appropriate professional supervision, has already been shown to exert striking benefits to children of primary school age in areas where water fluoridation is not practiced. This approach is being further expanded to determine whether the benefits of topical application in mouthpieces augment those already existent in areas where community water supplies are fluoridated. A related

study of considerable promise is examining the benefits which the topical mouthpiece method may provide to even smaller, pre-school children who have not yet developed their adult dentition.

## Periodontal Disease

Clinical and field studies described last year continue with regard to the relationship between the various clinical signs of periodontal disease and its pattern of subsequent development, such that rational methods of clinical therapy, up to this point in time largely empirical, might be developed.

With the growing concern regarding the role of dental plaque in the etiology of dental caries has developed an increasingly attractive hypothesis that similar adherant masses of bacterial, food debris and gummy materials which comprise the plaque may, over a period of some years, be instrumental in initiating gingival inflammation, and ultimately, frank periodontitis. Research results have already indicated quite clearly that the organism or organisms involved in periodontal disease do not resemble the streptococci which are now being scrutinized with respect to caries. On the other hand, a specific filamentous microorganism has previously been isolated from human diseased gums, and has been shown in experimental animals to elicit a disease state closely resembling periodontal disease. This filamentous organism, Odontomyces viscosus, shares with cariogenic streptococci, their capacity for producing large amounts of gummy extracellular material which, as in the case of the streptococci, also tends to hold the organisms in close approximation to the tooth surface at and below gingival margin. Thus, while research continues with respect to the basic characteristics of this organism, increased emphasis is being given to the possibility that its occurrence and its deleterious effects may be facilitated and/or enhanced by pre-existing dental plaque containing cariogenic streptococci. These two aspects of the Institute's research effort, both bearing on dental plaque as the common denominator in caries and periodontal disease, are being carried on in close and effective collaboration.

Basic and clinical studies with respect to the biology of the gums and adjacent tissues continue to provide information which may ultimately contribute to preventive and therapeutic approaches to periodontal disease from the point of view of increasing host resistance to the infectious process. Major support will be given to the ongoing effort to define the nature of those factors, particularly intrinsic enzymes, involved in normal synthesis and breakdown of the major structural proteins of the gums, namely collagen and elastin. These functions are seriously disturbed in periodontal disease. Other basic studies,

including field programs in geographic epidemiology will also continue to better assess the role of systematic factors such as nutrition in determining host susceptibility and/or resistance to periodontal disease.

## Oral Cancer

Cancers primarly focused in the mouth include those stemming from oral epithelium, those arising from specific dental tissues (usually of an embryonic origin) and those arising from disordered growth and differentiation of the supporting bony structures of the jaws. By far the most serious in number and in consequence are those originating from aberrant growth of the oral epithelium.

Occasionally, white patches can be visualized on the surface of the tissues lining the cheeks, lip or tongue, and are generally classified as leukoplakia. This condition, though not perfectly defined, is generally accepted as being pre-malignant. During the past year, Institute scientists have embarked on a systematic study of the oral-mucas membrane, particularly with regard to the biological properties of normal and abnormal oral epithelium. Their efforts have now demonstrated that one variety of white patch, frequently mistaken for leukoplakia, is not associated with malignant change. This condition, termed leukodema, can be differentiated from leukoplakia by appropriate microscopic analysis.

Exploration of the unique properties of the oral mucous membrane appears essential to any ultimate understanding of the relationship between leukoplakia and malignant change. As a consequence, these studies will be continued and expanded with such deliberate speed as funds and manpower will permit.

## Growth and Development

Disorders of normal oro-facial growth are manifested as a spectrum of malfunction, ranging from the serious cleft palate to relatively harmless, if aesthetically dissatisfying malocclusions. Significant energy has been devoted by Institute scientists to the end of providing a more rational understanding of the genesis of these conditions. Particular emphasis continues in the area of induced developmental abnormalities of the face and jaws arising from experimental introduction of drugs and other substances into the pregnant animal mother. Of specific importance is the broadening effort in the Institute to apply these studies to non-human primate species in order to obviate confusion which may arise as a consequence of studies of lower and less immediate related forms.

Another aspect of great programmatic relevance has been that of exploration into the relationships between anatomical abnormalities in the mouth region and neurological deficits. Institute scientists have

demonstrated a constant though paradoxical association between form and function in children afflicted with certain distinct hypoplastic anomalies of the facial skeleton.

Programs for the future in this area continue to be that of systematic expansion, such that truly meaningful data may be accumulated regarding prenatal influence on facial growth and development and regarding the relationship between normal and aberrant oro-facial growth and other systemic disorders.

Of the increase requested for this activity, $125,000 will support five additional positions. Also included in the net increase is $31,000 for annualization of the 1968 pay increase, $10,000 for one extra day of pay in 1969, and $33,000 for centrally furnished services from the National Institutes of Health management fund.

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 4 | $49,000 | 4 | $50,000 | ... | +$1,000 |
| Other expenses..... | ... | 792,000 | ... | 794,000 | ... | +2,000 |
| Total..... | 4 | 841,000 | 4 | 844,000 | ... | +3,000 |

Program plans for 1968 and 1969

Support under this activity is required for research and development of an adhesive filling material that will bond chemically to the surface of the tooth. As part of a broad study of physical and chemical properties of synthetic and biological adhesive materials, various substances, including marine biological adhesives, are under investigation.

Research emphasis will focus on the development of more effective reconstructive materials and techniques for the repair or replacement of structures lost as a result of dental or oro-facial diseases and conditions. This research will be accomplished through collaborative activities with other Federal institutions, such as the National Bureau of Standards, other non-Federal organizations, and private industry.

The development of effective tooth implants will be pursued. Emphasis will be placed on the development of implantation procedures designed to overcome the immunologic rejection response and permit permanent, effective functioning of the implanted teeth.

Included in this net increase is $1,000 for annualization of the 1968 pay increase and $2,000 for centrally furnished services from the National Institutes of Health management fund.

Biometry, Epidemiology and Field Studies

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 22 | $242,000 | 22 | $245,000 | .. | +$3,000 |
| Other expenses..... | .. | 190,000 | .. | 190,000 | .. | ..... |
| Total..... | 22 | 432,000 | 22 | 435,000 | .. | +3,000 |

Program plans for 1968 and 1969

This activity supports the Institute's scientific staff in the planning and conducting of biometric and epidemiological studies to test the hypotheses regarding factors incluencing incidence, severity and genetic patterns of oral diseases and conditions.

Emphasis will be placed on field trials of new or improved means, agents and technics so urgently needed if such diseases and conditions are to be better diagnosed, controlled and ultimately prevented.

Large-scale clinical trials of recently developed caries-preventive agents and methods will be continued to provide the scientific basis for improved public health programs in preventive dentistry.

Field investigations will also be conducted on oral cancer, oral-facial abnormalities which cover not only hereditary factors but also the effect of environmental elements, and development of new findings from basic and clinical research to the point where their application in general practice may be demonstrated.

There is a net increase of $3,000 which represents annualization of the 1968 pay increase.

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 39 | $364,000 | 40 | $384,200 | +1 | +$20,200 |
| Other expenses..... | .. | 283,000 | .. | 321,000 | .. | +38,800 |
| Total..... | 39 | 647,000 | 40 | 706,000 | +1 | +59,000 |

This activity provides support for the administration of the Institute's grants programs, which include research grants, fellowships, and training grants. The National Advisory Dental Research Council, and staff are responsible for the planning, development, review, and evaluation of the various extramural programs of the Institute. Continuous surveillance of scientific activities and progress is maintained as well as recording and reporting of fiscal and scientific data relevant to all transactions.

Reorganization of the extramural programs area along categorical program lines has given this area a significantly increased role in the Institute's total mission.

The increase requested for this activity will provide one position and $35,000 for its support. Included in the net increase requested is $1,000 for one extra day of pay in 1969, $4,000 for annualization of the 1968 pay increase, and $19,000 for centrally furnished services from the National Institutes of Health management fund.

## Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 26 | $263,000 | 27 | $275,000 | +1 | +$12,000 |
| Other expenses..... | .. | 140,000 | .. | 164,000 | .. | +24,000 |
| Total..... | 26 | 403,000 | 27 | 439,000 | +1 | +36,000 |

This activity provides support for the Director of the Institute and his immediate staff who are responsible for the over-all program planning, direction, coordination and administration of the Institute. The administrative functions include management in the areas of finance, personnel, supply, travel, space utilization and management analysis.

One position and $20,000 is requested to strengthen Institute program planning and evaluation. Included in the net increase is $3,000 for annualization of the 1968 pay increase and $13,000 for centrally furnished services from the National Institutes of Health management fund.

WEDNESDAY, MARCH 20, 1968.

# NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

## WITNESSES

DR. G. DONALD WHEDON, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. BENJAMIN T. BURTON, ASSOCIATE DIRECTOR FOR PROGRAM ANALYSIS AND SCIENTIFIC COMMUNICATIONS, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
W. GILBERT BAYLIS, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 6,359 | 6,798 | 7,343 |
| Positions other than permanent | 196 | 227 | 230 |
| Other personnel compensation | 33 | 41 | 42 |
| Total personnel compensation | 6,588 | 7,066 | 7,615 |
| Personnel benefits | 688 | 779 | 819 |
| Travel and transportation of persons | 236 | 330 | 345 |
| Transportation of things | 54 | 62 | 64 |
| Rent, communications, and utilities | 178 | 195 | 200 |
| Printing and reproduction | 59 | 95 | 100 |
| Other services | 740 | 994 | 1,100 |
| Project contracts | 4,627 | 7,278 | 7,278 |
| Payment to "National Institutes of Health management fund" | 5,766 | 6,388 | 6,464 |
| Supplies and materials | 1,210 | 1,249 | 1,270 |
| Equipment | 855 | 852 | 860 |
| Grants, subsidies, and contributions | 111,585 | 117,074 | 120,392 |
| Subtotal | 132,586 | 142,362 | 146,507 |
| Quarters and subsistence charges | −18 | −18 | −18 |
| Total obligations | 132,568 | 142,344 | 146,489 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 683 | 697 | 737 |
| Full-time equivalent of other positions | 19 | 22 | 22 |
| Average number of all employees | 661 | 687 | 712 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,263 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | | | |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 90,653 | 94,777 | 97,546 |
| (b) Fellowships | 6,077 | 6,591 | 6,737 |
| (c) Training | 14,855 | 15,706 | 16,109 |
| Total grants | 111,585 | 117,074 | 120,392 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 13,079 | 14,352 | 15,042 |
| (b) Collaborative research and development | 2,160 | 7,587 | 7,599 |
| (c) Biometry, epidemiology, and field studies | 571 | 713 | 721 |
| (d) Review and approval of grants | 1,936 | 2,247 | 2,311 |
| (e) Program direction | 328 | 371 | 424 |
| Total direct operations | 18,074 | 25,270 | 26,097 |
| Total program costs, funded [1] | 129,659 | 142,344 | 146,489 |
| Change in selected resources [2] | 2,909 | | |
| Total obligations | 132,568 | 142,344 | 146,489 |
| Financing: | | | |
| Comparative transfers to other accounts | 940 | | |
| Unobligated balance lapsing | 2,167 | 1,610 | |
| New obligational authority | 135,675 | 143,954 | 146,489 |
| New obligational authority: | | | |
| Appropriation | 135,687 | 143,954 | 146,489 |
| Transferred to other accounts | −12 | | |
| Appropriation (adjusted) | 135,675 | 143,954 | 146,489 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 132,568 | 142,344 | 146,489 |
| Receipts and other offsets (items 11-17) | 940 | | |
| Obligations affecting expenditures | 133,508 | 142,344 | 146,489 |
| Obligated balance, start of year | 76,065 | 77,807 | 88,651 |
| Obligated balance, end of year | −77,807 | −88,651 | −103,640 |
| Adjustments in expired accounts | −2,848 | | |
| Expenditures | 128,918 | 131,500 | 131,500 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 60,958 | 61,200 | 61,500 |
| Out of prior authorizations | 67,960 | 70,300 | 70,000 |

[1] Includes capital outlay as follows: 1967, $681,000; 1968, $852,000; 1969, $890,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $2,710,000; 1967, $5,619,000; 1968, $5,619,000; 1969, $5,619,000.

Mr. FLOOD. We now have the National Institute of Arthritis and Metabolic Diseases. The presentation will be made by Dr. G. Donald Whedon, the Director.

We will insert at this point in the record the biographical sketch of Dr. Whedon.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

(The sketch follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Name: Dr. G. Donald Whedon.

Position: Director, National Institute of Arthritis and Metabolic Diseases (NIAMD).

Birthplace and date: Geneva, N.Y., July 4, 1915.

Education: A.B., 1936, Hobart College; M.D., 1941, University of Rochester School of Medicine; Sc.D. (honorary), 1967, Hobart College.

Experience: Director, NIAMD, 1962–present; Assistant Director, NIAMD, 1956–62; Chief, Metabolic Diseases Branch, NIAMD, NIH, 1952–65; physician, Outpatient Department, New York Hospital, 1947–52; assistant physician, Outpatient Department, New York Hospital, 1944–47; assistant professor of medi-

cine, Cornell University Medical College, 1950–52; instructor of medicine, Cornell University Medical College, 1944–50; assistant in medicine, University of Rochester School of Medicine; and assistant resident physician in medicine, Strong Memorial Hospital, 1942–44; interne in medicine, Mary Imogene Bassett Hospital, Cooperstown, N.Y., 1941–42.

Association memberships: Association of American Physicians; the Endocrine Society (postgraduate committee, 1962–65); American Rheumatism Association; American Diabetes Association; American Federation for Clinical Research; New York Academy of Sciences; American Association for the Advancement of Science; American Medical Association; American Physiological Society; the Gerontological Society; American Institute of Nutrition; Pan American Medical Association; and American Gastroenterological Association.

Special awards, citations, or publications: Certified, American Board of Internal Medicine, 1950; assisted DGMS in organizing program of multicategorical clinical research centers in leading American medical institutions, 1959–61; Subcommittee on Calcium, Committee on Dietary Allowances, Food, and Nutrition Board, National Research Council, 1959–64; Editorial Board, Journal of Clinical Endocrinology & Metabolism, 1960–67; Editorial Board, Calcified Tissue Research, 1967–present; consultant to Space Medicine Division, Office of Manned Space Flight, NASA, November 1963–present; Scientific Council of the Maryland Academy of Sciences, March 1965–present; principal investigator of calcium-nitrogen metabolic balance study on NASA Gemini-VII space flight, December 1965.

Dr. Whedon is the author of nearly 50 scientific papers on metabolic and physiologic studies of convalescence, immobilization, paralytic poliomyelitis, diseases of bone particularly including osteoporosis, human energy metabolism, and space medicine.

Mr. FLOOD. I see you have a statement, Doctor. How do you wish to proceed?

Dr. WHEDON. If you will, Mr. Chairman, I would be pleased to read my statement and answer questions at any point during the reading and thereafter.

## GENERAL STATEMENT

Dr. WHEDON. Mr. Chairman and members of the committee, I am pleased to appear before you again to report on the progress of the National Institute of Arthritis and Metabolic Diseases and to discuss our needs for the fiscal year 1969. I would like to enumerate to you some of the encouraging developments in the large number of areas for which this Institute bears responsibility, which include, among others: arthritis and connective tissue diseases, diabetes and other metabolic disorders, diseases of the gastrointestinal tract, and diseases of the blood, bone, liver, kidney, and skin. In order to present you with an adequate description of the research findings of Institute scientists and grantee investigators we have prepared detailed special reports of progress in the Institute's major disease areas. In my present statement I shall mention briefly some of the highlights of the efforts of the previous year.

### ARTHRITIS

The sum total of recent experimental findings points to the likelihood that rheumatoid arthritis is the end result of a disturbance in the patients' defensive immune reactions which is directed against his own joint linings. Studies suggest that this disturbance may be induced by a previous infection by micro-organisms such as mycoplasma or certain viruses. A new instrument, called an arthroscope, has been developed which permits direct visual examination and biopsy of intrajoint structures, an extremely effective diagnostic procedure which obviates in

many cases undesirable exploratory surgery and which is superior to previously used "blind" biopsy techniques. In gout research an Institute scientist in Bethesda has discovered a specific enzyme defect in certain patients with a form of this painful joint disease.

DIABETES

Important new findings in this widespread metabolic disease involve the mechanisms which trigger the normal release of insulin in the body; whereas previously it was believed that insulin release from the pancreas was almost wholly dependent upon elevated blood sugar (glucose) levels, it has now been demonstrated that three gastrointestinal hormones are normally involved in initiating insulin secretion by the pancreas after the ingestion of food. Other findings involve the various as yet unclarified actions of insulin in the body and on the cellular level, and the effect of obesity on blood insulin levels in diabetic and normal individuals. A new type of diabetes in children has also been discovered which may be more common than has been recognized previously; it is manifested chiefly by growth retardation and failure to thrive and is based on a defect in glucose transport by the cells of the intestine and kidneys.

METABOLIC DISEASES

The term "metabolic diseases" encompasses a huge variety of disorders, ranging from diabetes which affects about 4 million Americans, to comparatively rare diseases such as maple syrup urine disease and sulfite oxidase deficiency.

Mr. Flood. Maple syrup?

Dr. Whedon. Yes, sir; the term given to this disease is based on the fact that some unusual substance is excreted by these patients which gives the very distinctive odor of maple syrup to the urine. This is a disease which occurs very early in life; the infant in the first week or two has difficulty in taking food and fails to grow; the mother is first aware, I think, on that basis and then notes the peculiar odor of the urine which is very sweet and reports this to the physician. This is how the diagnosis is made.

In many cases these metabolic diseases have been found to be the basis of mental retardation and early death in children. During 1967, Institute scientists and grantees have identified the specific biochemical defect in four such diseases, named for the enzyme found to be lacking in each disorder.

New important research findings have been obtained in cystic fibrosis, another inherited metabolic disorder which appears in an estimated 1 of every 1,000 to 2,000 newborn infants. Of particular importance to eventual solution of this disease was the discovery that a substance in saliva and sweat of cystic fibrosis patients causes animals to produce saliva with a high salt content. Since the sweat and saliva of cystic fibrosis patients also have an abnormally high salt content, the identification of this substance may point the way toward elucidation of the inherited molecular defect in this tragic disease.

GASTROENTEROLOGY

Probably the most significant recent accomplishment in gastroenterology was the successful transplantation of livers into four young girls, all of whom were able to live for 3 to 6 months after the operation. The success of this grant-supported graft research is attributed to judicious use of the relatively new antilymphocyte serum, to improvements in organ storage, and to better tissue typing and operating techniques.

LIVER TRANSPLANTS

Mr. FLOOD. Everybody has been excited by the great interest generated by the news media on the heart transplant. The committee has had recent testimony on the problems that presents. We heard that many competent surgeons can actually make a heart transplant; it is the rejection problems afterward that present the challenge. But now we get the impression that there is much more to this on the transplant of a liver.

Dr. WHEDON. From the purely technical point of view, as far as the surgery of putting the liver of one patient into the body of another, I would hesitate to say that there was more difficulty in comparison with other transplants. It is in the matter of the acceptance of the new tissue by the body, wherein lies the real problem, one which is common to all types of transplantation. But, in addition to that, in the liver there is a matter of the viability of the liver cells. These cells are, I would suspect, more difficult to protect when the organ is transferred from the donor to the recipient.

Mr. FLOOD. It is being suggested as we progress further into the exciting field of transplantation of organs, that the rejection problems of the liver perhaps may be the most difficult of all.

Dr. WHEDON. This could well be. There have been only 10 liver transplants tried altogether.

Mr. FLOOD. I notice in very, very young females; what is peculiar about that?

Dr. WHEDON. The opportunity for transplantation presented itself in very young infants.

Mr. FLOOD. Why females?

Dr. WHEDON. I think that was pure accident. I do not believe there is any sex relationship here at all. The first patients were all within the very first few weeks or months of life, and most of them had a congenital absence of the bile ducts. One of the patients had a form of liver cancer. In these patients it was very clear that unless a new liver was provided, life just could not go on.

Mr. FLOOD. I understand the liver is a rather virile organ when it comes to taking care of itself as distinguished from other organs. It takes care of itself pretty well.

Dr. WHEDON. That is true to the extent that if as much as approximately two-thirds of the organ is removed because of damage or trauma or disease, the remaining one-third is able to grow again and expand and take over the function that was formerly carried out by the full organ. But with much less than that, the liver cannot regenerate.

Mr. FLOOD. Will you provide for the record at this point some comment on the functions and the purposes of the liver?

Dr. WHEDON. I shall be glad to, Mr. Chairman.

(The information follows:)

## THE LIVER

### ANATOMY

The liver is the largest gland in the body. In the adult, its normal weight is between 1,450 and 1,750 grams (about 3½ pounds), or about one-fourth of the body weight. It is an irregular, wedge-shaped organ, the peculiarity of its contour being largely the result of the pressure of adjacent structures, since the liver tissue is soft enough to be molded by them. The liver occupies the right uppermost part of the abdominal cavity.

The liver, the largest secreting organ in the body, has many functions, but precise knowledge concerning these is incomplete. It possesses a great degree of reserve functional capacity and has extraordinary regenerative power. The functional unit consists of a liver cell (parenchymal cell), ringed by bile capillaries and bathed in venous channels.

### CIRCULATION

Blood flow through the liver is estimated at 1,500 milliliter (3 pints) per minutes. Under normal resting conditions the portal vein supplies about 75 percent of the blood flow and the hepatic arterial system, the remainder. Both systems empty into the hepatic veins. Specialized capillaries of the liver, called sinusoids, form a lacunar network and connect with capillaries from the portal vein and hepatic artery. Kupfer cells, which are potential phagocytes, line the walls of the sinusoids.

Blood from the intestinal tract (incorporating the various nutrients absorbed there) is conveyed to the liver cells by the portal circulation. Blood leaves the liver by way of the hepatic vein, carrying with it any products of chemical transformations which had taken place in the individual liver cells. Liver cells also secrete into another drainage system—the biliary system.

### BILE

Bile serves both as an excretory product of the liver and as a vital aid to intestinal absorption. Bile is secreted by the hepatic cells and accumulates in the gallbladder during interdigestive periods. The dilute biliary secretion of the liver is concentrated in the gallbladder through selective reabsorption of water. Bile is formed continuously and is excreted from small canaliculi draining individual liver cells into larger bile capillaries and thence into the common bile duct and gallbladder.

Bile contains the bile salts sodium glycocholate and taurocholate, bile pigments, lecithin, and cholesterol. It does not contain digestive enzymes of importance, but is of extreme significance for proper digestion and absorption of fat by virtue of its efficient emulsifying action of fat-containing intestinal contents. In the absence of bile, neither undigested fat nor digested breakdown products of fat can traverse the intestinal barrier into the blood. The absorption of the fat soluble vitamins also depends on the presence of bile salts.

The bile pigments play no part in the digestive process. Bilirubin and biliverdin are hemoglobin breakdown products which are formed in the liver. The bile serves mainly as a pathway of excretion for these pigments, which lend their color to the feces.

Normally the liver converts significant amounts of cholesterol to bile salts, and bile constitutes a major route of disposal of this substance.

### LIVER FUNCTION

The liver may be looked upon as the main chemical factory of the body. It is engaged in a multitude of chemical transformations which cover a broad range from the utilization and conversion of individual nutrients derived from the intestinal tract to the detoxification of bacterial and other poisons. To be able to carry out literally thousands of biochemical reactions during these vital proc-

esses, the individual liver cell must be endowed with a multitude of specific organic catalysts (enzymes) which regulate and facilitate highly specific chemical reactions. The following is a mere superficial listing of the most important of the various liver functions: interconversion of the various sugars, storage of excess sugars in the form of glycogen (animal starch), maintenance of normal blood sugar levels during fasting by conversion of glycogen to glucose (and the constant addition of the latter to the circulation to replace blood sugar metabolized by the body's muscles), interconversion of carbohydrates, proteins, and fats as needed, de novo synthesis of essential body proteins, protein degradation, synthesis and degradation of fats and of cholesterol, degradation and utilization of alcohol, conversion and degradation of steroid hormones, production of the anticoagulant factor prothrombin from vitamin K, and metabolic conversions of exogenous (drugs, toxic products of intestinal bacteria, etc.) or endogenous substances which are harmful, to form more innocuous metabolites (detoxification). In addition, the liver serves as a major storage of specific essential substances such as glycogen, the fat soluble vitamins (A, D, and K), and trace minerals (copper, iron, and zinc).

## PATHOLOGY

Like any other organ, the liver is subject to a multitude of anomalies and pathologic states. These may vary from congenital abnormalities of position and form, through primary and secondary malignancies. One of the most common disease conditions is acute hepatitis, inflammation of the liver caused by infectious or toxic agents, characterized by jaundice and frequently by liver enlargement, usually accompanied by fever and other systemic manifestations. Infectious agents that may cause hepatitis include viruses, spirochetes, protozoa, and bacteria. Toxic agents include carbon tetrachloride, chloroform, and many drugs.

*Obstructive jaundice* is caused by "backing up" or reflux of bile into the bloodstream caused by intrahepatic or extrahepatic biliary obstruction. This may be caused by gallstones, neoplasms, parenchymal liver disease, and even certain drug reactions.

A not uncommon form of liver damage is fatty engorgement of the liver, an abnormality caused by chronic excessive alcohol intake; this condition is a forerunner of alcoholic cirrhosis (scarring and contraction) which is the end result of long-term alcoholic injury to the liver. Other types of cirrhosis may be the end result of biliary injury or of chronic liver disease due to infectious or toxic causes.

Malignancies of the liver may be primary, arising in liver cells or bile duct cells, or they may be of secondary origin. In the latter case they are caused by malignant cells from other parts of the body which have lodged in the liver and have initiated autonomously growing tumors there.

Another type of liver pathology is the end result of chronic metabolic disorders; in a number of these the liver becomes engorged with abnormal amounts of fats, glycogen, and amyloid.

Many pathologic states of the liver do not involve grossly discernible changes in its anatomy, but are based on *functional* defects, where the liver is unable to carry out one or more biochemical reactions which are essential for normal body function. Liver function defects may run the gamut from temporary or barely demonstrable impairments through serious permanent and ultimately fatal defects.

## LIVER TRANSPLANTATION

A well-functioning liver is essential for life. Certain congenital anomalies of the liver, acute overwhelming infections, irreversible toxic damage, multiple liver abscesses, irreversible end-stage cirrhosis, and primary neoplasms all represent life-threatening liver conditions usually irreversible and ultimately fatal, in which death could be avoided if a well-functioning normal liver from another recently deceased individual could take over the function of the impaired organ. The mechanical aspects of such transplantation of a normal liver from a dead donor to a host requiring it are not insurmountable; in fact the technical steps of such surgery have been well worked out both in experimental animals and in man.

The most weighty obstacle to a proliferation of this procedure is the one which so far has limited many other types of homologous organ transplants, namely the eventual rejection reaction (a defensive immune mechanism) of the host aimed at the foreign organ, which takes place in all cases except in organ ex-

change between identical twins. Recently a grantee of this Institute was succesful in transplanting livers into four children who faced death from various types of permanent liver impairment. Two of these patients died eventually 3 to 6 months after their life-prolonging liver transplants; two more are still alive after 6 months. At the present time the use of immunosuppressive drugs and of antihuman lymphocyte serum (which tends to counteract much of the host's white blood cell and antibody reaction) helps overcome to some extent the host's attempts at rejection of the transplanted foreign organ. These measures, however, as well as tissue typing techniques and better methods of matching immune-compatible organs and recipients, have not yet been perfected to the point where frequent uneventful acceptance of the organ by the host is assured. Thus, liver transplantation as a frequently used therapeutic modality still awaits enabling future developments.

Dr. WHEDON. Other important advances in gastroenterology include the development of a safe and valuable procedure for pinpointing the elusive site of gastrointestinal bleeding in certain patients, and the demonstration that delayed blood platelet aggregation may be an important causative factor in the bleeding disorders which often complicate alcoholic cirrhosis of the liver.

### KIDNEY DISEASE

The Institute's artificial kidney program has led to development of a technique for storing and reusing conventionally used artificial kidney equipment which reduces the cost and simplifies the work involved in performing hemodialysis in the home. Work on a new and unique hollow fiber capillary kidney is progressing according to schedule, and it has already been tried successfully on two patients. New special low protein diets have been introduced which, in conjunction with infrequent peritoneal dialysis, permit survival and significant rehabilitation in certain types of patients with renal failure without recourse to kidney transplantation or artificial kidneys. The Institute has also initiated regular publication of a current-awareness publication, "Artificial Kidney Bibliography," to facilitate communication and integration of research efforts in artificial kidney transplantation reseach.

### ENDOCRINOLOGY

Research accomplishments in this field are led by elucidation of the role played by a new hormone, thyrocalcitonin, in the body's calcium metabolism and by a novel method of diagnosis which pinpoints the site of small adrenal tumors without recourse to exploratory surgery.

My statement here today has only touched upon a few of the findings of the past year. These and many others are presented to you in greater detail in the special reports which have been prepared for the committee. It is my sincere belief that these achievements herald similar and perhaps even greater advances during the next 12 months.

### SUMMARY OF THE BUDGET

Mr. Chairman, I am submitting a request for $146,489,000 for 1969, an increase of $4,145,000 over the 1968 operating level of $142,344,000. Included are increases of $2,769,000 for research grants, $549,000 for training grants and fellowships, $690,000 for laboratory and clinical research, $12,000 for collaborative research and development, $8,000 for biometry, epidemiology and field studies, $64,000 for review and approval of grants, and $53,000 for program direction.

Thank you. I shall be happy to answer any questions.

SUMMARY OF BUDGET REQUEST

Mr. FLOOD. Your 1968 budget is $142,344,000, and the request for 1969 is $146,489,000. That is an increase of $4,145,000. There is the usual decrease in the number of research grants that you will be able to fund out of this request, but you plan 10 more fellowships and six more training grants.

I admit these are very small increases, but they are the first we have seen so far in this arena.

Dr. WHEDON. Mr. Chairman, I think that the figure that you find, 10 fellowships and six additional training centers, is the result of the arithmetical calculation of the numbers of these opportunities that results from adjustment of our budget figures. It does not mean actually, at least in terms of training, that we will be able to go out and initiate six new training centers. This is a net figure that results from some of our previous grants classified as new coming in for continuation on a competing basis, and being approved, and so on. This is the principal way in which the total number of grants appears to be increased without a significant change actually in our total activity.

Mr. FLOOD. Then things are not as they seem in the justification.

EXPERIMENTAL TRAINING PROGRAM FOR CLINICAL INVESTIGATION

In the justification you refer to "experimental training programs for clinical investigation." Is this something new?

Dr. WHEDON. I am quite certain I spoke of it last year. I am so certain because I rarely lose an opportunity to speak about it if I am given that opportunity.

Mr. FLOOD. You have it now.

Dr. WHEDON. Thank you, Mr. Chairman.

This is a program which we are conducting at a limited number of medical centers and medical schools, which is for the purpose of exploring new ways of producing and developing and training a clinical investigator who will be more sophisticated than the current breed, who will be thoroughly grounded in all the basic techniques and modalities of research at the laboratory level, and also will be a skilled clinician and able to combine the knowledge of these two systems of endeavor so that more efficient and more effective research with patients will be carried out.

We have now awarded grants to five institutions in the country, and they have been underway long enough—that is, three of them have—so that we are just beginning to see the results and do have real hope that the training of clinical investogators will be more effective than it has been in the past. This is the purpose of this program.

CYSTIC FIBROSIS

Mr. FLOOD. Last year this committee did very little earmarking in NIH, but we did earmark $2 million for research on cystic fibrosis. What progress report can you make on our earmarking these funds?

Dr. WHEDON. Mr. Chairman, the committee actually directed that $2 million of our total appropriation be devoted to research on cystic fibrosis so that we could place additional emphasis on this very serious disease. And we have indeed expanded our effort in this area, and we

were able to increase our efforts monetarily to the extent of a little more than $600,000.

In cystic fibrosis over the past year there have been some very definite developments which now give us real hope that we are making progress toward the day when we shall really understand the mechanism of this disease. We reported last year the finding of a factor in the blood of cystic fibrosis patients which had an effect to retard or destroy the normal action of the cilia in the respiratory tract of rabbits.

I will now proceed to this fiscal year in which you are particularly interested.

Mr. FLOOD. That is right; we want to know year by year.

Dr. WHEDON. I brought that in merely to show that there was the first glimmer of a break in finding a specific substance which would likely be responsible for the metabolic defects in this disease.

This year we found another factor, that the sweat of patients with cystic fibrosis, when injected into the duct of the parotid gland of a rat, will cause the saliva of the rat to have a high concentration of sodium; that is, have the increased concentration of sodium of the same sort that occurs in the saliva and in the sweat of patients with cystic fibrosis. In other words, there has been demonstrated the great likelihood that there is some factor which is made by cells of patients with cystic fibrosis which interferes with the reabsorption of sodium in the secretion of saliva.

Mr. FLOOD. Hereditary?

Dr. WHEDON. We suspect it is because of the strong pattern of hereditary transmission of the disease in patients. It is hereditary. If we can get a better identification of this substance, find out what sort of a protein it is, if it is a protein, we may eventually be able to tell just what the biochemical processes are that are responsible for it, and perhaps get a hint as to the genetic background for this material.

### GENETIC COUNSELING

Mr. FLOOD. What do you do about a genetic background once you find it?

Dr. WHEDON. At the present time there are two things that one can do when one finds a genetic abnormality in a disease. The one best known is known as genetic counseling.

If we are able to identify individuals who are carriers of a disease like cystic fibrosis, and if a man and woman wish to marry and we can establish the fact specifically that they are carriers and therefore would be likely to have children who would have cystic fibrosis, we can tell them this and give them their choice of whether they would want to have children or not.

Mr. FLOOD. How would you know whom to talk to? Everybody who wants to get married?

Dr. WHEDON. The day may come when we will be able to do this. For example, there is a test which has recently been designed which will analyze the sweat of newborn infants. It is of sufficient simplicity that one might be able to carry it out routinely so that when each newborn infant leaves the maternity ward, the parents would know whether or not their child was going to develop cystic fibrosis or was likely to be a genetic carrier of that disease.

Mr. FLOOD. What does that mean for the parents?

Dr. SHANNON. Mr. Flood, the point Dr. Whedon is trying to make is not that there would be genetic counseling in relation to this specific disease only but that there are a whole series of genetically transmitted diseases that can be identified now in the carrier state. So that at one point in time you could determine the extent of match or mismatch between husband and wife, not in relation to this alone but in relation to a whole array of things.

I would guess that in 10 or 15 years this is something that would be done to children in their late teens as part of a routine physical check.

Dr. WHEDON. If I may go a little beyond that, we can see in the future a number of things we can bring into action that will deal with so-called genetic or metabolic diseases of this sort. We think the day will eventually come when we can actually intervene in the genetic process, in the molecular biochemical processes of the body and can induce the synthesis of an enzyme which is missing in a particular disease, in other words actually correct the disease in the patient. This day is some time off; it is 20 or 30 years off. But there are a variety of things we can do along these lines now. We can, for example, supply the missing material or hormone in certain diseases, or we can withhold from the diet particular items of food that the body with one of these diseases is unable to take care of because of a missing enzyme. An example of that is phenylketonuria; by withholding a particular amino acid (phenylalanine) from the diet, which that patient cannot take care of properly, we can allow normal body growth and development of the nervous system to take place.

### RHEUMATOID ARTHRITIS

Mr. FLOOD. The small amount of progress you have made on rheumatoid arthritis is certainly disappointing. You have a statement on page 118 that attracted my attention.

> Rheumatoid arthritis, the most vicious and crippling of all, continues to be the subject of aggressive and productive investigation.

But the trouble is productivity in the last several years has not been dramatic. What about that?

Dr. WHEDON. The items I mentioned in my opening statement perhaps are not very dramatic. They do represent, though, steps in the steady progress toward conquest of this disease.

Mr. FLOOD. Look at that phrase—"the most vicious of all."

Are you spreading yourself too thin on things that are not so vicious?

Dr. SHANNON. No, sir. I think that our state of ignorance with relation to this disease is such that the present stage of investigation constitutes a fairly broad, free-ranging probe of a variety of ways of attempting to get at the underlying mechanism of the disease—possible infectious origin, immunological origin, things of that general sort. Lack of progress of a dramatic sort, relative to prevention and definitive cure, is distressing because one would like to cure one disease each year. But the development of knowledge of these complex diseases just does not happen that way.

I think the individual investigations are justified on the basis of the viciousness of the disease and its complexity. If you examine the variety of approaches that are being taken, you realize that the variety

stems from a lack of understanding of the underlying mechanism. Until this underlying mechanism is fully clarified, the ability to handle the diseases definitively will not be available.

I do not think that there has been great progress in this disease in any single year since I have been at NIH. On the other hand, our understanding of the disease now, as contrasted to when I came to NIH some 19 years or so ago, is of a different order of magnitude. We can handle it better, treat it better, we can forecast its coming, we have identified a series of research areas that warrant exploration, and Mr. Flood, that is about as good as you can do at this stage of development.

I would think the chances are quite good that when Dr. Whedon comes back next year he will have another series of small advances, on different fronts, that are all aimed at clarifying the disease.

Mr. FLOOD. I wanted you to be aware of the committee's concern.

Dr. WHEDON. I would just like to add that we are proceeding along a logical train or plan of research. In recent years the evidence has become more and more impressive that the disease in the joints is the end result of a defect in the way that the body's defense mechanisms perform. They seem to be either directed against some protein of the body's own manufacture or, more likely as we see now just in the last few years, this whole inappropriate immune response may be triggered by the invasion of some peculiar organisms, either viruses or small organisms known as mycoplasma, which are midway in size between bacteria and viruses.

So we are engaged in work in two directions with respect to this real possibility of progress in rhemmatoid arthritis. We are looking into the fundamental biochemical and physical characteristics of the way in which these organisms create infections; we are having real difficulty in culturing these organisms because they are very peculiar ones.

The other direction is in studies with patients, trying out certain drugs which are immunosuppressive, because it would be logical to see if immunosuppressive drugs would counteract this disease which is in theory an expression of an altered immune process.

### HEMOPHILIA

Mr. FLOOD. Do you have anything new to report on hemophilia?

Dr. WHEDON. In hemophilia during the last year we have found two new blood factors which are potent anticoagulants. Research goes on in the laboratory all the time trying to define more and more precisely the various steps that take place when bleeding occurs, what the protective reaction is of the body to bleeding. There are a series of biochemical steps which take place, and a number of factors which are important in coagulation have been found. Just this past year we found two new factors which are anticoagulant in their action. But I must say that these substances have so newly been discovered they have not been characterized as yet. All we know is when they are given to animals they cause bleeding.

Mr. FLOOD. Are you interested in the genetic potential of this condition to attack it? Are you going to counsel people about this too?

Dr. WHEDON. That certainly is part of the approach here in hemophilia, but fortunately we do have now some specific blood fractions which can be administered to patients with hemophilia which will protect them.

Mr. FLOOD. Is there a high incidence of hemophilia in the United States?

Dr. WHEDON. I do not have available, Mr. Chairman, the exact number.

Mr. FLOOD. The condition is in males; is it not?

Dr. WHEDON. The condition is limited to males.

Mr. FLOOD. And transmitted through the female.

Dr. WHEDON. Transmitted through the female; that is correct. The total number of patients is not large, but obviously when the disease hits, it is a very serious disease and in severe cases may cause a crippling of the joints and bleeding in the intestine and so on.

As I say, in recent years we have been able to develop a substance called antihemophilic globulin which can be administered to patients, particularly when they are going to have surgery or tooth extractions, which will protect them from what otherwise might be a fatal bleeding.

### DIABETES

Mr. FLOOD. How many kinds of diabetes can you identify?

Dr. WHEDON. There are two main types: The mature onset diabetes, which is usually of a modest degree, in which a rather small proportion of patients require insulin. They are usually able to be supported either by diet therapy or by the oral antidiabetic drugs. The other type is the juvenile type, which is usually more severe.

Mr. FLOOD. We have become acquainted with the oral treatment for diabetes. Now I hear of cases where Mr. X has been taking the injection for a number of years, then was placed upon oral treatment. He takes that for a number of years, and one day his doctor tells him he has to drop the oral and go back to the injection. Why would that happen?

Dr. WHEDON. The month-to-month or year-to-year variation in diabetes is part of the explanation. The other is that such a thing might happen most likely at a time of unusual stress. Infection most likely. For example, if a patient on oral drugs, well controlled, should develop pneumonia or have a severe injury of some sort or other, that patient might then have to go on insulin for a while until his condition was stabilized.

Mr. FLOOD. As I understand it, if you have diabetes it cannot be cured. You can control it to lesser or greater degree, but there is no such thing as what we layman call a cure for diabetes?

Dr. WHEDON. That is the situation at the moment.

Mr. FLOOD. Did you find some new type or kind of diabetes in very young children?

Dr. WHEDON. We did this past year and all I can say about it at the moment is that we have described it. It occurs with a very large liver, a huge abdomen, there is a thinning of the bones, a premature development of what we call osteoporosis and failure to grow well. We have found, to this extent, that there is a defect in the kidney tubule responsible for the excretion of glucose and also a defect in the intestine in the absorption of glucose.

Mr. FLOOD. You have identified this?

Dr. WHEDON. We have identified it in a relatively small number of patients and we are now going to be looking to see if there are more of them, and obviously to find out more about the disease.

ORGAN TRANSPLANTS

Mr. FLOOD. During these weeks of hearings we have spent some time on the dramatic heart transplants and other transplants. Should you now tell us anything further, Dr. Shannon, about organ transplants?

Dr. SHANNON. There is one statement that should be in the record that is not, Mr. Flood, and that is this large spate of transplants of lungs, kidneys, livers, and hearts being done experimentally on a fairly wide scale at the present time——

Mr. FLOOD. With animals?

Dr. SHANNON. Yes, sir. But the basic finding that permits this type of work to go forward is not the sudden acquisition of new surgical techniques, but rather, the ability to identify tissue antibodies, and the ability to type these in a manner somewhat similar to the way you type blood for transfusions.

These observations, all used as a practical matter for the first time 3 years ago, have led to this totally new capability. This is the reason why you see these organ transplants now in so many publications.

GASTROENTEROLOGY

Mr. FLOOD. Especially since we have not discussed gastroenterology in any detail, I think we should place your report on this subject in the record.

(The report follows:)

SPECIAL REPORT:
GASTROENTEROLOGY

Gastroenterology - the study of the gastrointestinal and biliary tracts, and associated glands - is as complex from the standpoint of the biomedical research investigator as it is from the point of view of the practicing physician. The diversity and magnitude of gastrointestinal disorders combine to place these diseases in a prominent position among the chronic and disabling afflictions occurring in man.

The National Institute of Arthritis and Metabolic Diseases (NIAMD) bears the responsibility for the Government's program of research in this field. A broad array of recurring ailments of the digestive tract is undergoing investigation; foremost among these are: peptic ulcer, ulcerative colitis, regional enteritis (ileitis), and such malabsorptive 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.

In a major, concerted effort to define relevant areas for further research and development, and to explore and foster collaborative efforts in this field, the NIAMD early this year co-sponsored, with the American Gastroenterological Association and the Digestive Disease Foundation, a conference in Bethesda on "Digestive Disease as a National Problem."

In addition to establishing guidelines and incentives for future research, the conference, attended by more than 70 prominent gastroenterologists and specialists in related areas from universities, government agencies, private practice and concerned industrial sectors, was equally instrumental in highlighting the impact of gastrointestinal diseases on the health and well-being of Americans. Data presented by the expert conferees documented the profound impact of these diseases on the American public, both in the number of people afflicted and the financial burden imposed as a result.

Figures presented at the conference by the Public Health Service's National Center for Health Statistics (NCHS), based upon an analysis of death certificates filed in 1964, for example, indicate that digestive disease was the primary cause of death in 163,000 Americans (9 percent) and a contributing cause in another 98,000 (6 percent). Interview surveys by the NCHS estimate that 3.4 million people were hospitalized in 1964 directly for digestive disease (a total of 29 million hospital days).

Chronic digestive conditions, according to the NCHS, affect 12. 8 million people, with 245 million days per year of restricted activity, and 86 million days of bed confinement. Altogether, diseases of the digestive tract (including cancer of these organs) are (1) the leading cause of hospitalization in the

general population, (2) the second major cause of days lost from work, and (3) the third leading cause of death.

In the past year, investigators receiving financial support from the NIAMD contributed numerous important research findings. Of most far-reaching significance are the gradually developing progress in the field of liver transplants, as well as new diagnostic and therapeutic procedures for gastrointestinal hemorrhage and ulcerative colitis.

Liver Disease and Transplantation:

The liver, largest single organ in the human body, performs a multitude of complex chemical tasks without which life cannot exist. The liver functions, for example, as a filter and clearing station for purification and detoxification of blood, as a storage house for certain nutrients (particularly sugars, certain minerals and vitamins), as a site of production of blood proteins and of antibodies, and as a secretory gland which aids both digestion and the removal of wastes. It is not surprising then that an organ of such complexity is also subject to a broad range of injuries and disease states. Prominent among these is the condition known as "cirrhosis", the end-stage of a progressive destructive process resulting from chronic alcoholism or repeated infections, but the liver is also the site of a host of other diseases of infectious, parasitic, nutritional, metabolic, obstructive, toxic, and malignant origin.

Previous research has demonstrated the surgical and anatomical feasibility of liver transplants. Survival time in these studies has been limited primarily by poor immediate postoperative liver function. The past year, however, has seen the first enduring liver transplants. NIAMD-supported scientists at the University of Colorado Medical Center reported successful liver transplantations in four children, two of the transplant recipients being alive as of this writing. Two of the transplants were performed last July, another in September, and the fourth, in October (1967). The investigators credited a combination of improved methods of immunosuppression, organ treatment and storage, tissue typing and organ:recipient matching, and operating technique for the newfound success.

To suppress tissue rejection, the investigators placed the patients on a regimen of antilymphocyte globulin (ALG) in combination with azathioprine and prednisone. Two of the donor livers were preserved prior to implantation with a newly devised hyperbaric storage technique combining the use of hypothermia (chilling) to 4° C., hyperbaric oxygenation at 4 atmospheres pressure, and low flow perfusion with diluted blood. Previous animal experimentation had shown that this type of liver preservation resulted in as good a graft after 8 hours as did immediate transplantation.

Although the long-term prognosis is unknown as yet, the fact that these liver transplants have continued to function long beyond that achieved in earlier transplants holds tremendous promise for the future.

Treatment of Hepatic Coma:

Hepatic coma is a life-threatening stage in overwhelming acute liver disease, characterized by a shut-down of liver function, progressive intoxication by ammonia, coma, and death. A major problem faced by physicians is the maintenance of victims of hepatic coma until their own livers, disabled by an overwhelming infection or chemical insult, can be restored to normal function. NIAMD grantees at Marquette University reported success in the past year in therapy of patients in hepatic coma through use of an extracorporeal hepatic support system utilizing a cadaver liver. Dramatic results were achieved, the investigators reported, in three of four cases. The procedure involved cannulating the patient's femoral artery and saphenous vein. Blood flows in this system from the femoral artery to a heat exchanger to elevate its temperature slightly. The blood then enters the cadaver liver through its hepatic artery and portal vein and, after exiting through the hepatic veins, is pumped back into the patient's saphenous vein.

In three instances the comatose patients became conscious and their own livers began to function well following the perfusion therapy. However, all subsequently died of causes not directly related to hepatic failure. The success of this perfusion procedure could, in the future, prove particularly beneficial to hepatitis victims who develop hepatic failure and coma following only a single acute injury and whose livers may heal to resume normal function when inflammation, infection, and increased metabolic demands have subsided. The technique, the scientists suggested, also may aid patients suffering from chemical injury to their livers, such as occurs in carbon tetrachloride poisoning; patients in liver failure following portacaval shunt operations; and, possibly, candidates for liver transplants - by improving their pre-operative condition, thereby improving the chances for a successful graft.

Wilson's Disease Therapy:

D-penicillamine, a chelating agent which promotes urinary copper excretion, is generally accepted as effective therapy for Wilson's disease, an inherited disorder of copper metabolism causing progressive neurologic and hepatic disease. Studies by Institute-supported scientists at the Albert Einstein School of Medicine have now demonstrated that prolonged daily administration of this agent can delay or even prevent development of clinical manifestations of Wilson's disease in genetically and biochemically predisposed relatives of patients with this disorder.

In their investigation, the scientists employed a low copper diet and one gram of D-penicillamine orally per day to treat 42 of 53 asymptomatic subjects who had the chemical abnormalities associated with the disease or a positive family history. All of the subjects were followed from 3 to 10 years, after which overt manifestations of Wilson's disease were found in the 11 untreated subjects (all of whom were under the care of other physicians), with death due

to the disease occurring in five cases. No significant manifestations occurred in any of the 42 treated subjects. Moreover, studies based upon the natural history of 121 known Wilson's disease patients indicated that at least 8 of the treated subjects would have developed symptoms.

Defect in "Bronze Diabetes" Found:

Idiopathic hemochromatosis (or bronze diabetes) is an uncommon, chronic and progressive disorder characterized by excess deposition of iron in the liver and other tissues, increased pigmentation of the skin, cirrhosis of the liver and pancreatitis and, in most cases, diabetes mellitus. Cornell University scientists supported by the Institute have described for the first time a specific metabolic defect in this disorder. Their investigation demonstrated that afflicted patients with idiopathic hemochromatosis are deficient in hepatic xanthine oxidase, an enzyme which releases iron stored in the liver.

In this study, liver samples obtained from five patients with hemochromatosis, six with cirrhosis, and seven patients without liver disease were analyzed for xanthine oxidase activity. Activity of this enzyme in the liver samples from those with cirrhosis and hemochromatosis was found to be below that of the control groups and in a number of cases, there was no evidence of any xanthine oxidase activity at all. This finding has led the investigators to propose that hemochromatosis may be the result of a genetic defect characterized by failure to develop normal amounts of hepatic xanthine oxidase. Currently, the scientists are continuing their analysis of this enzyme activity on liver samples from siblings and children of patients with hemochromatosis.

Diagnosis of Gastrointestinal Hemorrhage:

A major challenge confronting physicians constantly is the early diagnosis of the site of gastrointestinal bleeding. Recent studies have indicated that the source of such bleeding escapes detection in 15 to 40 percent of patients studied. Institute-supported investigators at the University of Pennsylvania have now found abdominal angiography to be a safe and valuable diagnostic procedure for pinpointing the site of gastrointestinal hemorrhage in patients who are actively bleeding at a rate of 0.5 cc/minute or more.

The technique involves use of a radio-opaque catheter (with a specially molded tip) that permits selective catheterization of almost any branch of the aorta. The catheter is introduced into the femoral artery and then, under fluoroscopic control, into the celiac axis and later into the superior mesenteric artery (two branches of the aorta which supply the gastrointestinal tract), accompanied by separate injections of a contrast material. After each injection,

serial x-ray film exposures are made every second for 18 seconds, processed immediately, and compared for slight changes.

Using abdominal angiography, the investigators were able to find the source of gastrointestinal bleeding in 18 of 21 patients studied, identifying such sources of blood loss as a mucosal tear near the gastro-esophageal junction, benign stomach ulcers, "stress ulcers" in a post-surgical patient, rupture of the spleen and rupture of a splenic artery aneurysm (a balloon-like expansion of an artery).

The procedure also was found to be of particular value in studying patients with cirrhosis of the liver and in detecting or excluding the presence of bleeding esophageal varices (abnormally dilated veins at the gastro-esophageal junction). Additionally, the investigators found that the procedure, which requires only 30 to 40 minutes, does not interfere with other methods of examination or required surgery. In fact, the investigators suggest, the procedure may aid the surgeon greatly by localizing the bleeding area and thus should complement conventionally used techniques, such as "upper GI series" (serial x-ray pictures following the swallowing of a radio-opaque, barium-containing drink) which may demonstrate a lesion but will not indicate whether it is actively bleeding.

Surgery for Dumping Syndrome:

A severe and disabling consequence of ulcer surgery is a condition known as the "dumping syndrome" which develops in approximately one third of those patients requiring partial stomach resection for peptic ulcer. This surgically-induced disturbance of pyloric function causes an inability to control the rate of stomach emptying and results in a painful sense of abdominal fullness, nausea, belching, profound weakness and trembling, profuse sweating, palpitations and at times sudden and massive diarrhea within a short time after the intake of most foods.

In the past year, Institute-supported scientists at the University of California College of Medicine at Los Angeles devised an effective remedial surgical procedure which should be considered for the patient in whom conventional diet and drug therapy has failed. In their study, the investigators observed four patients with symptoms so severe, following peptic ulcer surgery (vagotomy and pyloroplasty), that they could not continue in their usual occupations. Selecting two of the patients, the investigators interposed a 4 cc segment of small intestine in a reversed "tail-to-head" position between the stomach and duodenum. This segment simulated the function of the surgically-removed pylorus, the stomach's food outlet control valve, by slowing the downward movement of food. Although gastric retention was a problem in the immediate postoperative period, the dumping syndrome disappeared within a few days in both patients and has not recurred in 16 and 24 months, respectively.

Prior to attempting the technique on the two patients, the investigators conducted experimental trials in 10 dogs, who showed a marked reduction of symptoms following the surgical procedure. The scientists suggested that the jejunum interposition and reversal is an effective remedy for both the anatomical and physiological disturbances in the dumping syndrome after vagotomy and pyloroplasty.

Cell Replication and Gastric Ulcer:

In another important finding, an Institute grantee at Cornell University Medical College has shown that the failure of epithelial cell replication is of primary importance in the mechanism of stress ulcer formation in the stomach. Two years ago this same grantee made precise measurements of the life cycle of epithelial cells in the normal gastrointestinal tract, thereby providing a basis for comparing the kinetics of cell renewal in normal and disease states. In his recent study, he has now demonstrated that stress inhibits proliferation of young epithelial cells in the gastric mucosa, leading to a disporportionate loss of cells from the mucosa and to eventual local erosion and the phenomenon known as stress ulceration.

In this study, stress ulcers were induced in mice by placing them in restraint cages for 13 to 42 hours. Each animal was given an injection of radioactive thymidine sometime during this period, and one hour later, the rate of thymidine incorporation into new cells was determined. About 50 percent fewer cells became labeled with thymidine in the mucosa of animals under stress, compared to the mucosa of control animals, and slightly more than half of these were in metaphase, indicating a marked inhibition of new cell formation. Inhibition of cell proliferation occurred both before and during the appearance of the earliest pathologic abnormalities in the mucosa.

Malabsorption Syndrome:

Celiac disease, or nontropical sprue, is characterized by fatty diarrhea, intestinal malabsorption, and dietary deficiency symptoms, all caused by an intestinal sensitivity to the protein fraction gliadin, or gluten, in the diet.

In the past year, Institute-supported researchers at Johns Hopkins University demonstrated in a study of 16 cases of adult celiac disease that intestinal ulcerations - a severe, often fatal, and heretofore overlooked complication - must be added to the list of conditions which may interfere with the proper diagnosis. Their study described an adult celiac disease patient who, while on a gluten-free diet, developed intestinal ulcerations, stricture and perforation leading to death. Inquiry and literature review revealed 15 other such

patients, 12 of whom died under similar circumstances, indicating that such complications may prevent the usual good response to a gluten-free diet and thus obscure the diagnosis of celiac disease. The 37-year-old male patient had been in complete remission on a gluten-free diet for more than six years when he developed acute jejunal and ileal ulcers and intestinal obstruction. The ulceration could not be attributed to a specific infection, direct toxic effect of drugs, or any of the usual causes, and no form of medical therapy was effective in inducing a remission. The patient died subsequently following perforation of an ulcer.

In the 15 similar cases, it also appeared that such ulcerations were a complication of celiac disease, per se. Each of these patients had chronic diarrhea and intestinal malabsorption and, at surgery or autopsy, multiple ulcerations of the small intestine. Two improved after surgical resection of the multiple ulcerated areas and were alive and well two and six years later, respectively, indicating that early resection of the ulcers and obstructed areas may alter the subsequent course.

In the past year, grant-supported scientists at Harvard Medical School also have obtained evidence linking abnormal bile salt metabolism to the malabsorption seen in conditions characterized by unusual proliferation of the normal bacteria in the small intestine. In the past, several studies have implicated abnormal bile salt metabolism in the pathogenesis of such disorders, but the mechanism producing such malabsorption heretofore has not been defined.

The Harvard researchers have now demonstrated the presence of unconjugated bile salts in the jejunal fluid of two patients with fatty stools and bacterial overgrowth of the small intestine. The normal colonic bacteria found proliferating in the gastrointestinal tracts of these patients were capable of unconjugating normally-produced conjugated bile salts secreted by the liver. Conjugated bile salts are a necessary component of normal intestinal absorption of fat and, therefore, the change induced by the bacteria caused malabsorption of fats and fat-soluble vitamins. Therapy with appropriate antibiotics was found beneficial because it eliminated the bacteria capable of producing this effect.

Ulcerative Colitis:

One of the commonest chronically debilitating disorders of the gastrointestinal tract is ulcerative colitis, a progressive, inflammatory disease of the colon or large bowel. Of unknown etiology, the disease is characterized by severe cramps, repeated bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals. Although the disease continues to resist efforts to discover its cause, progress is being gradually achieved in therapy which is aimed primarily at correcting mineral and nutrient loss, controlling diarrhea, preventing infection, and ministering to the patients' psychologic needs.

During the past year, research performed by Institute grantees at the Yale University School of Medicine, suggested a possible link between milk intolerance and ulcerative colitis. Milk intolerance, a relatively common syndrome in certain otherwise normal adults and in patients with inflammatory bowel disease, is known to result in many cases from a deficiency of the intestinal enzyme lactase which converts lactose or "milk sugar" into glucose and galactose. In their investigation, 39 patients with ulcerative colitis or proctitis were studied to determine whether in any way lactose intolerance might be a factor which contributes to diarrhea in ulcerative colitis patients. Their study showed that 59 percent of the patients were found to have lactose intolerance. Follow-up evaluation 6 to 16 months after institution of a lactose-free diet showed that the only patient with lactose intolerance who did not have a major remission during the study had failed to follow the prescribed lactose-free diet. The results indicate that the inflamed, irritated bowel of ulcerative colitis patients cannot handle the osmotic load, and that lactose intolerance imposes an extra burden upon the inflamed bowel. On the basis of their study, the investigators advise a lactose-free diet in ulcerative colitis patients who also have lactose intolerance. Although this study does not necessarily implicate intestinal lactase deficiency as a causative factor in ulcerative colitis (this deficiency may be secondary to the underlying prime disorder, and, in fact, intestinal lactase deficiency is known to develop as an aftermath of a number of other primary debilitating diseases), this finding opens up a new, promising approach to better symptomatic treatment of patients with ulcerative colitis.

Milk Intolerance and Lactase Deficiency:

During the previous two years, Institute-supported researchers have traced the cause of milk intolerance in certain otherwise normal adults and in patients with inflammatory bowel disease to a deficiency in the intestinal enzyme lactase, which converts lactose or "milk sugar" into its simple sugar components glucose and galactose. Since then, increasing evidence has been found that intolerance to milk is a relatively common syndrome in adults.

Last year Institute grantees demonstrated that milk intolerance based on lactase deficiency is much more common in Negro adults than in the adult white population and suggested that intestinal lactase activity may be genetically controlled. Such studies have been expanded recently to cover children between the ages of 1 and 11. In one such study conducted by Institute grantees at Johns Hopkins University School of Medicine, 40 healthy children, 20 white and 20 Negro, randomly selected from a pediatric comprehensive care clinic were investigated. Lactose loading in this group produced abdominal discomfort in seven Negro children and two white, and 14 of the 20 Negro and 2 of the

20 white children had a family history of milk intolerance. It was also found that lactose-induced symptoms in Negro children and adults increased in frequency with advancing age, suggesting a gradual decrease in lactase activity after weaning. This was not as common in the white subjects studied.

Similar studies have also been carried out by Institute grantees at the University of Oklahoma Medical Center. Both the Johns Hopkins study and the Oklahoma studies indicate that there is a distinct racial difference in lactase activity and that a genetically determined intestinal lactase deficiency is responsible for the majority of instances of milk intolerance found in adults.

These studies have considerable diagnostic and therapeutic significance, with particular import for Negro patients presenting with a variety of gastrointestinal symptoms, such as diarrhea, nausea, and abdominal pains, which do not appear to be related to any specifically manifest pathologic lesion. In view of these findings, it becomes necessary to rule out, in such patients, the presence of milk intolerance or lactase deficiency (a diagnosis not arrived at often in adults at present). Once this diagnosis is confirmed, dietary restriction of milk, milk products, and foods containing milk sugar (lactose) usually leads to the cessation of the distressing symptoms.

Outlook

This resume of but several research investigations and progress in the broad field of gastroenterology illustrates the productivity and diversity of the numerous studies supported by the Institute. The significant accomplishments of the past year in the treatment and prevention of liver disease, peptic ulcer, and ulcerative colitis give renewed hope for improved therapeutic modalities in the foreseeable future.

Mr. FLOOD. Mr. Casey?

CYSTIC FIBROSIS

Mr. CASEY. Dr. Whedon, I note you followed the instructions of the committee on cystic fibrosis, and in fact allocated more than the committee suggested. I think you have already answered the chairman that there are breakthroughs coming that encourage further development of this research. Is that right?

Dr. WHEDON. That is correct, sir.

I would, if I may, expand a little bit. I wonder if you are aware of the fact that about 1 month ago we had a 3-day conference in New York City, jointly sponsored by this institute and by the National Cystic Fibrosis Research Foundation, which brought together about 100 investigators from many different disciplines to review the current state of the disease and to examine in real depth two new particular breakthroughs. I mentioned one last year and one this.

As a result of the workshops and the intense discussion we had, there will be, I am quite sure, close cooperation among investigators to try to exploit these so-called breakthroughs and see if we cannot find out exactly what enzyme or hormone defect there is that is responsible for this extraordinary excretion of sodium that takes place in the sweat and the saliva. Then one day, I hope it will not be too far off, we will find some way of inhibiting or perhaps correcting this obvious defect.

I am sure you are aware that cystic fibrosis is a lot more complicated than just the abnormal sweat excretion. The problem of thickened secretions in the lungs and from the pancreas is also a serious problem.

I should mention that the head of our own cystic fibrosis group in Bethesda this year found that the secretion of calcium in saliva is unusually high in these patients and that the saliva combines with the glycoproteins, the so-called sugar proteins of the secretions, to form an insoluble compound or precipitate. So this may be one of the ways in which the secretions are made unusually thick and interefere with normal function.

Mr. CASEY. It is something you are not going to find a cure for, but you are going to find some way to control it, is it not?

Dr. WHEDON. I think at the present time that is the best estimate we can make. Obviously the more we learn about the disease, the more we dig into the biochemical abnormalities and try to characterize them, the more likely we are to find ways of influencing the disturbed physiology of this disease. Really, this has been a sort of a hopeless problem for a long time, but, sincerely, I think some findings have been uncovered now within the last 2 years that really give us some hope.

Mr. CASEY. I am glad to hear that and wish you continued progress on it.

Thank you, Mr. Chairman.

JUSTIFICATION MATERIAL

PUBLIC HEALTH SERVICE

National Institute of Arthritis and Metabolic Diseases

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $143,954,000 | $146,498,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 175 | Research | | $94,777,000 | | $97,546,000 | | +$2,769,000 |
| | General research support grants | | (9,551,000) | | (9,409,000) | | (-142,000) |
| | Scientific evaluation and planning | | (20,000) | | (20,000) | | (0) |
| | Categorical clinical research centers | | (1,500,000) | | (1,500,000) | | (0) |
| 133 | Fellowships | | 6,591,000 | | 6,737,000 | | +146,000 |
| 135 | Training | | 15,706,000 | | 16,109,000 | | +403,000 |
| | Direct Operations: | | | | | | |
| 137 | Laboratory and clinical research | 538 | 14,352,000 | 571 | 15,042,000 | +33 | +690,000 |
| 143 | Collaborative research and development | 29 | 7,587,000 | 29 | 7,599,000 | | +12,000 |
| 152 | Biometry, epidemiology and field studies | 27 | 713,000 | 27 | 721,000 | | +8,000 |
| 154 | Review and approval of grants | 80 | 2,247,000 | 85 | 2,311,000 | +5 | +64,000 |
| 155 | Program direction | 23 | 371,000 | 25 | 424,000 | +2 | +53,000 |
| | Total obligations | 697 | 142,344,000 | 737 | 146,489,000 | +40 | +4,145,000 |
| | Unobligated balance, reserve | 4 | 1,610,000 | | 0 | -4 | -1,610,000 |
| | Total, obligations and balance | 701 | 143,954,000 | 737 | 146,489,000 | +36 | +2,535,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 697 | 737 | +40 |
| Full time equivalent of other positions..... | 22 | 22 | 0 |
| Average number of all employees..... | 687 | 712 | +25 |
| 11 Personnel compensation: | | | |
| Permanent positions..... | $6,798,000 | $7,343,000 | $+545,000 |
| Positions other than permanent..... | 227,000 | 230,000 | +3,000 |
| Other personnel compensation..... | 41,000 | 42,000 | +1,000 |
| Total personnel compensation..... | 7,066,000 | 7,615,000 | +549,000 |
| Personnel benefits..... | 779,000 | 819,000 | +40,000 |
| 21 Travel and transportation of persons.... | 330,000 | 345,000 | +15,000 |
| 22 Transportation of things..... | 62,000 | 64,000 | +2,000 |
| 23 Rent, communications and utilities..... | 195,000 | 200,000 | +5,000 |
| 24 Printing and reproduction..... | 95,000 | 100,000 | +5,000 |
| 25 Other services..... | 994,000 | 1,100,000 | +106,000 |
| Project contracts..... | 7,278,000 | 7,278,000 | 0 |
| Payment to "National Institutes of Health management fund"..... | 6,388,000 | 6,464,000 | +76,000 |
| 26 Supplies and materials..... | 1,249,000 | 1,270,000 | +21,000 |
| 31 Equipment..... | 852,000 | 860,000 | +8,000 |
| 41 Grants, subsidies, and contributions.... | 117,074,000 | 120,392,000 | +3,318,000 |
| Subtotal..... | 142,362,000 | 146,507,000 | +4,145,000 |
| Deduct quarters and subsistence charges..... | -18,000 | -18,000 | 0 |
| Total obligations by object..... | $142,344,000 | $146,489,000 | $+4,145,000 |

## Summary of Changes

| | |
|---|---|
| 1968 Enacted appropriation | $143,954,000 |
| Unobligated balance reserve | -1,610,000 |
| Total estimated obligations, 1968 | 142,344,000 |
| 1969 estimated obligations | 146,489,000 |
| Total change | +4,145,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annalization of new positions authorized in 1968 | ... | ..... | ... | $60,000 |
| 2. Annalization of 1968 pay increase | ... | ..... | ... | 95,000 |
| 3. One extra day of pay in 1969 | ... | ..... | ... | 21,000 |
| Subtotal, built-in | ... | ..... | ... | 176,000 |
| Program | | | | |
| 1. Research grants | ... | $94,777,000 | ... | 2,769,000 |
| 2. Fellowships | ... | 6,591,000 | ... | 146,000 |
| 3. Training grants | ... | 15,706,000 | ... | 403,000 |
| 4. Laboratory and clinical research | 538 | 9,468,000 | 33 | 525,000 |
| 5. Review and approval of grants | 80 | 937,000 | 5 | 30,000 |
| 6. Program direction | 23 | 258,000 | 2 | 20,000 |
| Subtotal, program increase | | | 40 | 3,893,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| C. Centrally furnished services from the National Institutes of Health management fund: | | | | |
| 1. Laboratory and clinical research | ... | $4,884,000 | ... | $34,000 |
| 2. Collaborative research and development | ... | 38,000 | ... | 6,000 |
| 3. Biometry, epidemiology and field studies | ... | 43,000 | ... | 1,000 |
| 4. Review and approval of grants | ... | 1,310,000 | ... | 15,000 |
| 5. Program direction | ... | 113,000 | ... | 20,000 |
| Subtotal management fund | ... | ..... | ... | 76,000 |
| Total change requested | ... | ..... | +40 | +4,145,000 |

Explanation of Changes

Research grants--The net increase of $2,769,000 is the result of an increase of $2,911,000 for regular research projects offset by a decrease of $142,000 for general research support grants. Due to the general increased average costs, however, the total avialable funds will provide support for 55 fewer regular research projects.

Fellowships--The increase of $146,000 will provide for an estimated additional 10 fellowships in 1969.

Training grants--The increase of $403,000 will provide for an estimated additional 3 new training centers.

Laboratory and clinical research--The increase of 33 positions and $525,000 will provide for initiating new studies and for strengthening of clinical investigations and laboratory studies in the fields of arthritis, gastroenterology, endocrinology, hematology and metabolic diseases including diabetes.

Review and approval of grants--The increase of 5 positions and $30,000 will provide for strengthening of grants management and analysis activities.

Program direction--The increase of 2 positions and $20,000 will provide a modest strengthening of Institute management staff

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301--Research and Investigation, in general..... | Indefinite |
| Title IV, Part D--National Institute on Arthritis, Rheumatism and Metabolic Diseases..... | Indefinite |

PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume V.

The Public Health Service Act, Title IV, National Research Institutes, Part D, National Institute on Arthritis, Rheumatism, and Metabolic Diseases, National Institute on Neurological Diseases and Blindness, and other Institutes.--

"Sec. 431 (a) The Surgeon General shall establish in the Public Health Service an institute for research on arthritis, rheumatism, and metabolic diseases...."

"Sec. 433 (a) Where an institute has been established under this part, the Surgeon General shall carry out the purposes of section 301 with respect to the conduct and support of research relating to the disease or diseases to which the activities of the institute are directed, through such institute and in cooperation with the national advisory council established or expanded by reason of the establishment of such institute. In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions."

Justification

National Institute of Arthritis and Metabolic Diseases

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 697 | $7,845,000 | 737 | $8,434,000 | +40 | +$589,000 |
| Other expenses | -- | 134,499,000 | -- | 138,055,000 | -- | +3,536,000 |
| Total | 697 | 142,344,000 | 737 | 146,489,000 | +40 | +4,125,000 |

The National Institute of Arthritis and Metabolic Diseases bears responsibility for a broad array of diseases characterized by their chronicity and long-term disabling effects rather than mortality: various arthritic diseases and related rheumatic and connective tissue disorders, diabetes and other inherited errors of metabolism, diseases of the gastrointestinal tract including diseases of the liver and gallbladder, endocrine disorders, diseases of the blood and bone, urological and kidney diseases, and such fields as orthopedic surgery, dermatology, and nutrition.

The total program necessarily includes studies of a fundamental nature as they are associated with the specific disease objectives described above. Thus, the Institute has an important stake in the pursuit or support of research in fundamental sciences which constitute the foundation of knowledge pertinent to any of the above disease categories: Chemistry, biochemistry, enzymology, molecular biology, anatomy, histology, pathology, physiology, medicinal chemistry, pharmacology, toxicology, and genetics.

The Institute's efforts in support of fundamental research are conditioned by the type of diseases within its sphere of interest, and are based on the hardheaded realization that no major progress in solving these health problems results without specific advances in the fundamental disciplines deeply involved with each disease.

The Institute, therefore, endeavors to maintain a rational balance in the allocation of its funds and efforts among clinical studies, fundamental investigations and, where the opportunity is ripe for exploitation, specifically directed, planned developmental research.

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Research projects..... | $83,706,000 | $86,617,000 | +$2,911,000 |
| Special programs..... | 11,071,000 | 10,929,000 | -142,000 |
| Total research grants..... | 94,777,000 | 97,546,000 | + 2,769,000 |

Introduction

The National Institute of Arthritis and Metabolic Diseases (NIAMD) supports more than 2,300 studies and research projects at over 425 research-oriented institutions, including universities, medical centers, and hospitals throughout the country. These studies cover the broadest array of disease categories of all the Institutes of the National Institutes of Health. The principal objectives of these diverse research studies receiving grant support from this Institute are to increase our understanding of normal life processes as the basis for understanding disease, to identify the causative agents and faulty biochemical mechanisms that create disease conditions, to improve therapeutic modalities, and to discover means of prevention of many, varied diseases.

Foremost among the disease categories within the research interest of the Institute are the various forms of arthritis and related connective tissue disorders; diabetes and other metabolic diseases both inherited and acquired; endocrine disorders; gastroenterological diseases, such as peptic ulcer, regional enteritis, ulcerative colitis, and diseases of the liver and gallbladder; bone diseases; blood disorders; diseases of the kidney and urological disorders; dermatological diseases, and the fields of nutrition and orthopedic surgery.

Many of these maladies are prime contributive causes of death, such as diabetes, certain gastrointestinal diseases, and kidney diseases. In the main, however, they are lingering, chronic and debilitating diseases which impose an awesome burden on their victims physically, psychologically, and economically.

In the coming year, Institute support of research will continue to focus on the 10 Program Areas--arthritis, diabetes, endocrinology, gastroenterology, hematology, metabolism, dermatology, urology, nutrition, and orthopedics--which comprise its Extramural Programs, with special emphasis in those areas and disease categories in which more fruitful research may be expected.

In addition, in the years ahead the Institute will become increasingly active in the support of research with clinical application in the field of organ transplantation, involving particularly the liver, the kidneys, the intestines, and glands of internal secretion. This long-range research effort is aimed at developing the ability to transplant an entire normal organ, such as the kidney and liver, as well as portions of organs and internally secreting glands, such as the pancreas, not only as replacements for non-functioning,

diseased organs but also for therapeutic amelioration of hormonal deficiencies and inherited enzyme defects which cause disease.

Arthritis and Related Diseases

Program emphasis in this field of research will continue to be given to determining the causative agents or factors in arthritic disorders of unknown etiology, to improving existing methods of treatment and management, and to discovering means of preventing them.

A primary objective will be rheumatoid arthritis, by far the most devastating and crippling of all the arthritides. In support of this goal, this Institute will continue the research efforts of a new program, initiated last year, known as the Experimental Clinical Research Program in Rheumatoid Arthritis. The program involves studies of (1) the etiology of rheumatoid arthritis, particularly as related to infectious agents, and (2) clinical research, with particular attention to evaluation of new treatments.

In the coming year, particular emphasis will continue to be given to studies into the relationship to rheumatic diseases of promising new etiologic possibilities which have implicated a viable organism. Particular attention will be paid to the mycoplasma, a group of organism as yet incompletely studied, for which problems of isolation and identification remain the primary obstacle. Thorough investigation also will be made of viruses of the genus Bedsonia. Arthritis was produced in monkeys recently by injecting them with Bedsonia organisms isolated from human patients with Reiter's syndrome, a disorder related to rheumatoid arthritis

Specific goals in the coming year will include studies and support of research on the possible etiologic relationship of viable agents to certain rheumatic diseases, especially inflammatory diseases of connective tissue, rheumatoid arthritis, systemic lupus erythematosus and polyarteritis. Planning also calls for the development of suitable experimental animal models, as well as extension of present knowledge of the role of basic immune mechanisms and the possible role of lysozymes in these diseases. Studies on the mechanical function of joints and their lubrication mechanisms also will be emphasized, as will studies on the early diagnosis of gout.

Research into bone metabolism as it relates to bone fractures and degenerative bone diseases, such as osteoarthritis, also will be pursued.

Diabetes

An inherited metabolic disease, diabetes, which afflicts an estimated 4 million Americans, is a major area for research support by this Institute. Research on this disorder has in recent years passed through a phase which saw significant therapeutic advances, notably the development of oral anti-diabetic drugs for effective blood sugar control in middle-aged and elderly diabetics without recourse to daily injections of insulin. Institute support in this area of research now and in the immediate future will focus on broadly-based, fundamental investigations which will lead us closer to the discovery of the underlying cause of diabetes.

The most obvious defect in diabetes is the inability to utilize carbohydrates normally for energy. Underlying the disease is a basic impairment of insulin activity. Institute support of diabetes research in the coming year will stress studies into the mechanism of insulin secretion and the impairment of insulin activity as a result of physiologic, chemical, endogenous or exogenus inhibitors or antagonists, as well as investigations to ascertain the specific genetic factors which make some individuals more susceptible to this disease than others.

Also contemplated by the Institute in the coming year is the extension of specific studies designed to improve present methods of treatment and control and investigations aimed at avoiding or controlling the development of the serious neurological and vascular complications of diabetes.

In 1969, Institute planning also will focus on studies designed to improve procedures and methods for early detection of prediabetic individuals (those genetically predisposed to the disease, but as yet not displaying its signs and symptoms) with a view toward eventual development of methods for postponement of the emergence of the overt disease.

Other Inherited Diseases of Metabolism

Although diabetes is the most prevalent and widely known of the inherited metabolic diseases, there are many other such disorders for which the Institute serves as the focus of research support. Among these are cystic fibrosis, phenylketonuria, Wilson's disease, galactosemia, alcaptonuria, histidinemia, homocystinuria, familial Mediterranean fever, the various glycogen storage diseases, congenital nonhemolytic jaundice, and many others.

Institute support of research in cystic fibrosis, characterized by an abnormality in the products of all glands which secrete fluid to external body surfaces, has lead to a number of significant advances. Foremost among these was the finding that sweat and saliva from children with cystic fibrosis introduced into the salivary gland duct of rats caused a marked increase in rat salivary sodium output (a phenomenon characteristic of cystic fibrosis). The implications of this finding are most important in that they suggest that an unknown but probably specific substance is present in the secretions of children with cystic fibrosis which causes the excessive salinity of sweat and saliva. Future studies will be directed at isolation and identification of this unknown factor. Other research will pursue a factor in the blood of cystic fibrosis patients which has been shown to interfere with the normal sweeping action of the cilia of the respiratory tract.

An example of productive research in the area of inborn errors of metabolism last year was the finding by Institute-supported investigators that prolonged daily administration of D-penicillamine, a chelating agent that promotes urinary copper excretion, can delay or even prevent the development of clinical manifestations of Wilson's disease in genetically and biochemically predisposed relatives of patients with this disorder; without this treatment relatives usually develop the disease. Wilson's disease, an inherited disorder of copper metabolism, causes progressive neurologic and hepatic disease and is ultimately fatal.

Overall, in the coming year, the Institute's program of support in the area of inborn errors of metabolism will emphasize basic studies designed to advance existing knowledge of intracellular processes of metabolism, including protein synthesis and enzyme regulation and their genetic control. Research support also will stress investigations to improve current methods of diagnosis and treatment.

Metabolic and Endocrine Disorders (unrelated to genetics)

Major areas of research receiving Institute support in this category include studies of the nature and function of the glands of the endocrine system--the adrenals, thyroid, parathyroid and pituitary glands. The study of normal and abnormal endocrine function not specifically disease oriented encompasses a spectrum of problems since the endocrine system, along with the nervous system, controls virtually all the metabolic, reproductive and growth functions of man and higher animals. Thus, it is obvious that any one specific hormonal activity or deficiency will interrelate with and affect profoundly an unlimited number of biological reactions.

Current understanding and accepted methods of treatment of hyper- and hypothyroidism, for example, result from detailed knowledge of thyroid hormones and of the pituitary hormone, thyrotropin, which affects the endocrine output of the thyroid gland. Similarly, fundamental research which led to the isolation and purification of the pituitary human growth hormone (HGH), although still limited in supply, now makes it possible for a small number of children afflicted with hypopituitary dwarfism to attain improved growth through HGH replacement therapy.

Institute support will continue to place emphasis on the search to overcome the critical problem of species-specificity-the fact that in many cases a hormone derived from one species of animal will not exert its biological effect when administered to a member of another species. Knowledge of the molecular structure variations associated with hormones from different species will facilitate discovery of what part of a hormone constitutes the "active core" (which may be common to the various hormones from different species) and, perhaps, make it possible to modify the structure of hormones of animal origin so as to promote their effectiveness for treating human endocrine disorders. Knowledge of what constitutes the "active core" of a hormone also is essential to develop a method for laboratory synthesis of hormones for therapeutic use in endocrine diseases.

Support of research in this area in the coming year also will stress studies in glucagon and insulin synthesis and action, and in the fast developing field of neuroendocrinologic control, the latter designed to isolate and purify a number of "releasing factors", substances originating in the hypothalamus of the brain which are transmitted to the adjacent pituitary and stimulate the release of specific pituitary hormones into the individual's general circulation. It is essential that progress continue toward the isolation and purification of these factors.

In 1969, Institute emphasis will be placed on expanding studies on the precise mechanisms by which hormones influence metabolism and how they cross-react with each other; studies to synthesize in the laboratory hormones of known structure and their known molecular fragments and to elucidate the as yet unknown structure of other hormones and to synthesize them; and studies to develop more sensitive and reliable chemical and biological assays for the amounts of hormones circulating in patients with suspected endocrine disease.

Such research is of great pertinence since the mechanism of hormone action really is germaine to all disease in as much as they affect the metabolic process of all tissues of the body.

Gastroenterology and Liver Disease

Broadly speaking, the basic objectives of Institute-supported research in the complex area of gastroenterology are to increase scientific and clinical understanding of the fundamental processes of digestion, absorption, secretion, excretion and other functions of the gastrointestinal tract, the liver, pancreas, and gallbladder both in health and in disease. Such basic knowledge is essential to improving the treatment of the diseases of the gastrointestinal tract and its organs, as well as for the development of improved understanding of its normal metabolic and physiologic processes.

Institute emphasis will again be placed on specific studies and research projects dealing with the physiology and diseases of the stomach, small intestine, and the liver. Studies in acute liver failure will be aimed at developing extracorporeal treatment systems to "carry" such patients until their own livers heal sufficiently to resume normal function (for instance, circulating the patient's blood through the isolated liver of a large experimental animal until his own liver regains its ability to function). Some success in this approach was reported last year by Institute grantees and the technique warrants continued investigation. Similarly, dramatic success was scored by Institute-supported investigators in the field of liver transplantation in the past year. In this significant advance, these investigators successfully transplanted livers into four young girl patients who had lost their own liver function, all of whom were alive and reasonably healthy three to six months after the transplants. The four patients, ranging from 13 months to 2 years in age, were suffering from disorders which usually are fatal; three, from biliary atresia (a congenital absence of bile ducts); and one, from liver cancer. The success achieved with these liver transplants was attributed by the investigators to the judicious use of a relatively new antilymphocyte serum fraction and to improved organ storage procedures, tissue typing and operating techniques.

Continued strong Institute support also is contemplated in research on peptic ulcer disease, ulcerative colitis, regional enteritis (ileitis), and related digestive tract diseases, as well as studies in malabsorption disorders, such as celiac disease, and investigations seeking new diagnostic, therepeutic and preventive procedures for the broad spectrum of ailments that afflict the digestive tract.

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Kidney and Urologic Disease

Planned research support by this Institute in the coming year in kidney and urologic diseases will strengthen previous efforts to increase the understanding of and to improve therapeutic modalities and means of prevention of diseases of the genitourinary tract. Other research support will be directed to the expansion of current knowledge and understanding of the ultimately fatal uremic syndrome in end-stage kidney failure.

Institute support of research in this area will stress kidney transplantation as a means of long-term replacement therapy, with particular emphasis on development of effective means of organ storage and preservation. The increasing success in the field of kidney transplantation more than warrants the continuation of a strong and vigorous program of support in this area.

Other clinically important areas in urology that will receive increased Institute research support include problems of painful urination, urinary stone formation, obstructions of the urinary tract, diseases of the prostate and endocrine relationship to prostatic hypertrophy, and urinary tract infection. Another area that will receive Institute support involves the congenital abnormalities of the lower genitourinary tract in children and the related development of kidney disease in later life. Such research, it is hoped, will lead to improved means of detection, treatment and management.

Hematology

The primary objectives of this Institute's continuing and multi-faceted program of research support in hematology are to promote an improved understanding of diseases of the blood and their basic causes, to discover better diagnostic procedures and methods of treatment and prevention, and to clarify the role played by blood factors and elements in coagulation and cert in immunity reactions.

Among the more fruitful and productive areas of research being pursued intensively are red blood cell production and anemias, immunological aspects of transplantation, other immunology reactions, blood coagulation, drug reactions, and hemoglobin synthesis. Specifically, areas of research to receive support in the coming year include development of antihemophilic factor preparations for treating hemorrhage in hemophilic patients and for prophylaxis prior to elective surgery, as well as studies in the genetic transmission of hemophilia, sickle cell anemia and other hereditary blood diseases; Rh compatibility, blood clotting, immunologic aspects of the coagulation disorders, and investigations of the composition, structure and characteristics of serum proteins and fibrinogen, thrombin and hemoglobin.

In the search for improved knowledge of blood disorders, sickle cell anemia, an inherited disease widespread in the United States, is illustrative of the role played by fundamental research. Its cause, discovered only several years ago, was found to be due to a change in the molecular structure of an abnormal type of hemoglobin in red blood cells which cause them to twist into a sickle shape. In their changed shape, the "sickled" blood cells cannot roll freely through very small blood vessels, leading to a variety of symptoms and death. Having found the cause, scientists supported by this Institute are now seeking to discover better methods of detection of the disease, and of

prevention of sickling. Already the life span of victims of this disorder has been increased considerably through antibiotic drug therapy to counteract the many frequent infections found intercurrent with this disorder.

Dermatology

The primary interest of most investigators in this still underdeveloped field of research continues to focus on the growth, structure and function of skin as vital to any future research progress. Overall, the support of research in dermatology by the Institute in the coming year will emphasize the extension of clinical and laboratory investigations in both normal and abnormal skin, and studies designed to relate certain cellular malfunctions to specific chemical disturbances in order to gain a better understanding of the etiology and pathogenesis of skin diseases.

Emphasis also will be placed on the continuation and expansion of ongoing studies on the effectiveness of the various cytotoxic (anti-cancer) chemotherapeutic agents in severe and disabling psoriasis, and the search for chemotherapeutic agents which might be effective in the treatment of other skin disorders. Psoriasis, a common skin disorder characterized by an abnormal local proliferation of skin cells, is being studied by an increasing number of scientists since it provides a model for other, related research in skin disorders.

An increasing amount of research will involve the study of biosynthetic pathways of the skin and the process of epidermal keratinization, which is expected to shed ultimately new light on psoriasis and ichthyosis. New insight into the possible mechanism of certain bullous skin diseases has been gained by immunologic studies which should lead to an improved understanding of the nature of pemphigus and certain other skin diseases.

Nutrition

Although interest in nutrition research is spread throughout many of the National Institutes of Health, the NIAMD is the major focus of research support in this area, providing approximately 58 percent of all extramural support. Research in nutrition is difficult to categorize with any precision since it is closely related to and directly concerned with many areas of study such as metabolism, endocrinology, and gastroenterology. About 50 percent of research supported in this area, however, relates to the following six major categories: deficiency-induced states, the nutritional and metabolic based for cardiovascular disease, fats and fatty acids, malabsorption diseases and the specific requirements for actions of and metabolism of vitamins and trace elements, proteins and carbohydrates.

Specifically, Institute support of research in nutrition in the coming year will stress studies on the interrelationship between carbohydrate, fat, and protein metabolism, and expanded studies on the effects of qualitative and quantitative variations in the diet on body composition, appetite regulation and food intake.

## Research Grants Program Analysis

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| 1. Arthritis | $ 6,750,000 | $ 6,990,000 | +$240,000 |
| 2. Dermatology | 1,850,000 | 1,910,000 | +60,000 |
| 3. Diabetes | 4,750,000 | 4,920,000 | +170,000 |
| 4. Endocrinology | 12,600,000 | 13,040,000 | +440,000 |
| 5. Gastroenterology | 9,300,000 | 9,620,000 | +320,000 |
| 6. Hematology | 6,500,000 | 6,730,000 | +230,000 |
| 7. Metabolism | 21,500,000 | 22,250,000 | +750,000 |
| 8. Nutrition | 6,800,000 | 7,030,000 | +230,000 |
| 9. Orthopedics | 3,600,000 | 3,720,000 | +120,000 |
| 10. Urology and kidney diseases | 6,100,000 | 6,300,000 | +200,000 |
| 11. Other or interrelated areas | 3,956,000 | 4,107,000 | +151,000 |
| 12. Subtotal | 83,706,000 | 86,617,000 | +2,911,000 |
| 13 General research support grants | 9,551,000 | 9,409,000 | -142,000 |
| 14. Scientific evaluation and planning | 20,000 | 20,000 | 0 |
| 15. Categorical clinical research centers | 1,500,000 | 1,500,000 | 0 |
| 16. Total obligations | 94,777,000 | 97,546,000 | 2,769,000 |

## Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting continuations | 1,650 | $57,214,000 | 1,624 | $60,125,000 | -26 | +$2,911,000 |
| 2. Competing projects | 369 | 13,688,000 | 356 | 13,188,000 | -13 | -500,000 |
| 3. New | 382 | 11,663,000 | 366 | 11,163,000 | -16 | -500,000 |
| 4. Supplementals | (123) | 1,141,000 | (230) | 2,141,000 | (+107) | +1,000,000 |
| 5. Subtotal regular program | 2,401 | 83,706,000 | 2,346 | 86,617,000 | -55 | +2,911,000 |
| 6. General research support grants | | 9,551,000 | | 9,409,000 | | -142,000 |
| 7. Scientific evaluation | | 20,000 | | 20,000 | | 0 |
| 8. Categorical clinical research centers | | 1,500,000 | | 1,500,000 | | 0 |
| 9. Total research grants | 2,401 | 94,777,000 | 2,346 | 97,546,000 | -55 | 2,769,000 |

Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Fellowships..... | $6,591,000 | $6,737,000 | +$146,000 |

The fellowship program is designed to increase the number of individuals trained for research and related teaching in the biomedical disciplines and clinical research areas that fall within the purview of this Institute. Through this program fellowships are awarded to outstanding scientists preparing for careers in research to support part of the cost of the necessary academic training and research experience.

The Postdoctoral Fellowship program is a primary mechanism to bring about the increase in number of individuals trained for research and teaching by providing support directly to selected individuals, training may be taken at any institution in the United States or abroad which is qualified to provide the necessary facilities and direction. One of the special advantages of this type of award is that it may be unique in character or content and, thereby, be a contributing first step in evolving an important future research field.

The Research Career Development program provides an advance form of fellowship to support more extended training and development of a limited number of individuals who show outstanding talent and a promise of significant biomedical research contributions as independent investigators.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting..... | 212 | $3,545,000 | 218 | $3,645,000 | +6 | $100,000 |
| b. Competing..... | 51 | 745,000 | 52 | 760,000 | +1 | 15,000 |
| 2. Supplementals..... | (4) | 20,000 | (4) | 20,000 | 0 | 0 |
| 3. New..... | 199 | 2,281,000 | 202 | 2,312,000 | +3 | 31,000 |
| 4. Total fellowships..... | 462 | $6,591,000 | 472 | $6,737,000 | +10 | 146,000 |

Fellowships (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Postdoctoral..... | 210 | $1,700,000 | 215 | $1,750,000 | +5 | +$50,000 |
| 2. Special..... | 104 | 1,300,000 | 106 | 1,325,000 | +2 | +25,000 |
| 3. Research career: | | | | | | |
| a. Career..... | 28 | 780,000 | 28 | 780,000 | 0 | 0 |
| b. Developmental..... | 120 | 2,811,000 | 123 | 2,882,000 | +3 | +71,000 |
| 4. Total fellowships..... | 462 | $6,591,000 | 472 | $6,737,000 | +10 | +$146,000 |

Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Training Grants..... | $15,706,000 | $16,109,000 | +$403,000 |

As a result of its responsibilities for the largest number and greatest variety of diseases, this Institute is the principal focus at NIH of support for training in clinical departments of medical schools and centers. The basic problem confronting the Institute and which this program deals with is the inadequate number of independent clinical research investigators and teachers having the necessary competence and scientific sophistication required for effective biomedical research and to engage in research training. The situation applies to the well established fields of research interest, such as arthritis, diabetes and endocrinology, and in even greater degree to emerging or resurgent areas of research interest, such as dermatology, orthopedics, urology and gastroenterology.

Immediate and long-range goals emphasize attracting, training and retaining within biomedical research and academic careers able, imaginative clinical researchers and teachers in numbers sufficient to pursue and train for present and anticipated promising research opportunities. The eventual clarification, treatment, management and prevention of disease problems depends on continued, competent investigative pursuit. In response to the long training-time problem, the Institute has established a limited number of "Experimental Training Programs for Clinical Investigation." These programs have demonstrated the manner in which medical schools with an excellent record of research productivity are able to solve the problems of earlier identification of and greater in-depth training in fundamental research for outstanding physicians better than can be accomplished through the usual categorical training program.

## Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting.... | 251 | $12,230,000 | 255 | $12,506,000 | +4 | +$276,000 |
| b. Competing..... | 32 | 2,196,000 | 34 | 2,318,000 | +2 | +122,000 |
| 2. Supplementals..... | (18) | 420,000 | (18) | 425,000 | (0) | +5,000 |
| 3. New..... | 20 | 800,000 | 20 | 800,000 | 0 | 0 |
| 4. Scientific evaluation | (1) | 60,000 | (1) | 60,000 | (0) | 0 |
| 5. Total training grants. | 303 | 15,706,000 | 309 | 16,109,000 | +6 | +403,000 |

## Training Grants (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate..... | 303 | $15,646,000 | 309 | $16,049,000 | +6 | +$403,000 |
| 2. Scientific evaluation. | (1) | 60,000 | (1) | 60,000 | ( ) | 0 |
| 3. Total training grants. | 303 | 15,706,000 | 309 | 16,109,000 | +6 | +403,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 538 | $6,360,000 | 571 | $6,854,000 | +33 | $+494,000 |
| Other Expenses..... | | 7,992,000 | | 8,188,000 | | +196,000 |
| Total..... | 538 | 14,352,000 | 571 | 15,042,000 | +33 | +690,000 |

Introduction

The major objectives of the Institutes's intramural program are:

1) To develop more complete information about fundamental mechanisms in chemical and physiological sense of how cells grow, divide and control their activities.

2) To employ this knowledge to discover the mechanism by which diseases develop and incapacitate man.

3) To discover methods of therapy and prevention for those diseases for which the Institute is responsible.

The total program is extremely broad, encompassing both basic and applied research, and is designed to overcome the lack of fundamental knowledge in such disease categories as arthritis and related rheumatic and connective tissue disorders, diabetes and other inborn errors of metabolism, gastroenterology, diseases of the endocrine system, renal and urological diseases, and blood, bone and skin disorders, among others.

In support of the basic mission of the NIAMD, therefore, Institute research necessarily emphasizes studies and projects in the fundamental sciences as they are related to the previously-mentioned, specific disease categories, including chemistry, biochemistry, enzymology, molecular biology, anatomy, pathology, histology, physiology, medicinal chemistry, pharmacology, toxicology and genetics. Virtually all of the diseases within the purview of the NIAMD are closely related to, and require a thorough understanding of, metabolic processes--the multitude of biochemical reactions through which energy is provided for all bodily functions--, modulating effects of hormones on metabolism, the manner in which these metabolic processes are altered in specific diseases, and how aberations of normal metabolism may cause various diseases.

Arthritis and Rheumatism

Arthritis and rheumatism are broad terms applied to a large number of disease conditions, all of which inflame and destroy joints and affect tissues adjacent to the joints. Arthritis and rheumatic diseases are generally divided into 13 categories, foremost of which are: arthritis of unknown etiology, such as rheumatoid arthritis and ankylosing spondylitis; degenerative arthritis or osteoarthritis; connective tissue disorders, such as systemic lupus erythematosus; infectious arthritis; traumatic arthritis; and arthritis associated with biochemical abnormalities, such as gout. Each condition in every category is a distinct disease entity but all have one common denominator--symptoms in the joints or adjacent tissues.

In the past year, Institute research investigators have performed a great many difficult and ingenious laboratory and clinical studies designed to gain new knowledge and insights into the causes of these diseases. Rheumatoid arthritis, the most vicious and crippling of all, continued to be the subject of aggressive and productive investigations. Also receiving intensive investigation were Reiter's disease, Sjogren's syndrome, leukopenia in connective tissue disease, and systemic lupus erythematosus with renal complications.

Significant progress during the past year has been made by Institute scientists in further clarifying the nature of gout, an inherited metabolic disorder resulting from deranged metabolism of purines. In gout, uric acid, a breakdown product of purines, accumulates in the blood and body tissues either because of overproduction of the potentially harmful substance or because of failure to excrete it adequately via the urine. When uric acid accumulates as urate crystals in the joints (in many cases characteristically in and around the big toe) the result is gouty arthritis. Excessive uric acid production, Institute investigators found, is associated with enzyme defect. This finding is closely related to results of studies of the Lesch-Nyhan syndrome, a recently discovered metabolic and neurologic disease of young males. Children with this disorder while appearing normal at birth fail to develop normally, showing instead mental retardation, uncontrollable movements of the hands, and eventually compulsive self mutilation of fingers and lips. The investigators who first identified this peculiar neurological and behavioral disorder associated it with a biochemical abnormality. They found that children with this disorder produced six times more uric acid than normal for their body weight. These findings led Institute scientists to further investigation in hopes that discovery of the the biochemical basis for excessive uric acid formation in these children might provide leads to the primary biochemical derangement responsible for excessive uric acid formation in gouty arhtritis patients as well. After months of studies on Lesch-Nyhan victims, the Institute scientists identified the primary enzyme defect in these children, an absence of the enzyme hypoxanthine-guanine phosphoribosyltransferase (PRTase), which is involved in purine metabolism. Ordinarily, this enzyme's highest activity is in the brain, especially in the basal ganglia. Since the affected children's major neurological symptoms indicate dysfunction of basal ganglia, this suggests a cause and effect relationship.

The discovery of the primary defect in Lesch-Nyhan disease, as anticipated by the Institute scientists, provided new insight into the metabolic derangement in some gout patients. When they determined PRTase activity in blood cells of gout patients who produced an excess of uric acid, they found a markedly diminished activity of this same enzyme in a number of patients. Further, some of the gout patients (those with the least amount of PRTase

activity) also showed evidence of a neurological defect that had not previously been recognized as being related in any way to their known gout conditions. These investigations demonstrate that at least one form of gouty arthritis may be the end result of a specific enzyme defect which results in excessive amounts of uric acid in the blood.

Diabetes and Other Metabolic Diseases

Diseases of deranged metabolism represent a broad area of research responsibility for Institute investigators. Intensive, basic studies have been conducted by NIAMD scientists this past year in diabetes, the best known of this group of diseases, in the continuing search for the cause of the body's inability to utilize carbohydrates normally, and to clarify the true nature of diabetes. These investigations are designed to develop further knowledge of diabetes and of the normal role of insulin in various tissues and on the cellular level. Other studies by Institute scientists seek to elucidate further the nature of a postulated interference with normal insulin activity in diabetes and of the substances which can destroy or inactivate insulin after its release from the pancreas--a relatively new concept of "insulin antagonism" or blockage. This past year has also seen continuation of studies on the role played by growth hormone, adrenocorticotropin (ACTH), and the adrenal steroid hormones in the induction of diabetes in rats, the results of which are providing a better understanding of the complicated hormonal interrelationship in this disease.

Another metabolic disease undergoing exhaustive investigation by Institute scientists is cystic fibrosis (CF), a serious hereditary metabolic disease which affects the exocrine glands of the body (glands which excrete their products directly to the outer environment on into the lungs and gastrointestinal tract). Institute researchers are continuing to seek the precise mechanism responsibile for the production of the abnormally viscous mucus which characterizes many exocrine secretions in cystic fibrosis. Likewise the abnormally high electrolyte output of the sweat glands in cystic fibrosis is being investigated. New techniques of micropuncture of individual sweat glands are being used in these investigations in an effort to establish morphologically and functionally the specific nature of the defect in sweat electrolyte secretion.

During the past year, scientists of this Institute and the National Institute of Dental Research have obtained evidence that calcium combines with glycoproteins in submaxillary saliva of cystic fibrosis patients to form a precipitate which might cause obstruction of the gland's ducts. A similar phenomenon if found in other mucus secreting glands of the body in cystic fibrosis may explain many of the pathologic and clinical findings in this disorder. The observation that abnormal ionic concentration in CF may have an important effect on the solubility of glycoproteins has important implications in the pathogenesis of CF. This is especially true because an increase in calcium levels in many glycoprotein-rich biologic fluids is one of the most constant findings in cystic fibrosis.

Significant research by Institute scientists last year also identified a previously unrecognized disease and discovered its underlying biochemical sause. Called sulfite oxidase deficiency, the disease is characterized by severe neurological and mental retardation, dislocated eye lenses, and death in early childhood. The underlying biochemical abnormality is impaired activity of sulfite oxidase, the enzyme which normally catalyzes conversion of sulfite to sulfate. Sulfite oxidase deficiency joins two other causes of mental retardation, homocystinuria and cystahioninuria, as a disease of the metabolism of sulfur-containing compounds. The investigators who also discovered the fundamental biochemical defects in the other two diseases, are not attempting to learn how frequently sulfite oxidase deficiency occurs in the population at large and among mentally retarded children in particular, simultaneously, possible methods of prevention of the clinical abnormalities are being explored.

Institute researchers also discovered an enzyme defect in maple syrup urine disease, a familial metabolic disorder, characterized by progressive cerebral dysfunction and excretion of urine with an odor like that of maple syrup. Biochemically, victims of this disorder show elevated blood and urine levels of the amino acids leucine, isoleucine and valine and of their corresponding keto acids. The presence of these metabolites suggested a defect in the enzyme responsible for the further metabolism of these keto acids to carbon dioxide. Such a defect, the absence of the enzyme alpha-ketoisocaproic acid decarbonxylase, was demonstrated by these scientists in leukocytes and in fibroblasts grown from skin explants obtained from a child with this disorder. The absence of this enzyme helps explain the buildup of the aforementioned amino acids and their keto acids in the blood and urine of affected individuals.

Endocrinology

The field of endocrinology embraces broad studies of the internally secreting glands of the human body, such as the pituitary, thyroid, parathyroid and adrenal glands, their respective hormones, and the roles they play in the normal and abnormal physiology of the body. Hormones--specialized chemical messenger substances produced in the various endocrine glands are capable in some instances of modifying specific metabolic or physiologic reactions and in others of modulating the over-all rate of metabolic processes. Additionally hormones are primarily responsible for and control sexual differentiation of an individual before birth and, later, growth, intellectual development, vigor, reproduction and senescence. Thus, hormones regulate a broad spectrum of organ and body activities; abnormalities in hormonal action are the basis for a multitude of serious diseases.

Institute researchers are pursuing broad, intensive studies designed to elucidate precisely how hormones influence metabolism and other body functions and how they cross react with one another, as well as to clarify their molecular structure. Research projects also are under way which seek to develop feasible methods for chemical synthesis of hormones, especially the pituitary human growth hormone, and to modify other mammalian growth hormones so as to obtain fractions biologically active in man.

Osteoporosis is a bone thinning disorder which affects at least one of every five individuals over 50 years of age in the United States, primarily elderly women. It is believed to have result from hormonal and dietary factors combined with the inactivity of old age. The main dietary factor implicated in a long term defect in calcium intake over outgo. The most important dietary source of calcium in the American diet are milk and milk products. In the past year, Institute scientists obtained evidence that in some patients this defect may result principally from prolonged absention from milk ingestion instituted voluntarily to avoid symptoms of milk intolerance caused by a deficiency of the intestinal enzyme lactase. This enzyme is responsible for the orderly digestion of the milk sugar lactose. Its absence results in symptoms of milk sugar intolerance: gaseousness and bloating, flatulence abdominal cramps, pain and diarrhea

Although the number of osteoporotic patients studied was small, there was a manifesly significant difference in the prevalence of lactase deficiency between groups of osteoporotic and normal subjects. The investigators feel that long-term dietary calcium restriction voluntarily instituted to avoid milk intolerance symptoms may have accentuated greatly the loss of bone mineral leading to osteoporosis. This association between lactase deficiency and osteoporosis, they believe, could provide one biochemical basis for the development of osteoporosis in one segment of the elderly population.

In another important study in this area of research, Institute scientists in the past year have shown that a recently discovered hormone produced in the thyroid gland, thyrocalcitonin, lowers blood levels of calcium by inhibiting resorption of calcium from bone. This finding provides new and significant knowledge about the mechanism of action of this hormone and warrants further research into its physiologic role and possible therapeutic application.

Gastroenterology

The field of gastroenterology, which encompasses the study of the gastrointestinal tract, the biliary tract, and the associated organs, is as diverse as it is complex; it involves all the fundamental processes which enable the body to digest, absorb, secrete, and excrete all that it ingests and to perform other additional specialized functions of the liver. The extraordinary advances in knowledge of the physiological and clinical aspects of the myriad number of gastrointestinal diseases in recent years have been achieved only through a determined and sustained research effort.

In the past year, Institute scientists have conducted a number of clinical and laboratory investigations designed to improve our understanding of the factors involved in intestinal malabsorption and sprue diseases. Other studies were devoted to the clinical entity "protein-losing gastroenteropathy."

A long-term project by Institute investigators, designed to evaluate the pathologic physiology of Whipple's disease and to study the effect of therapy on its natural history, is providing insight into a form of intestinal malabsorption which appears to be caused by bacterial agent and which can be reversed by therapy developed by the staff.

Hematology

The field of hematology is another that presents an extremely broad category of research interest to this Institute. The many studies conducted by Institute researchers in this area are designed to improve current understanding and knowledge of the various blood disorders and their basic causes, and to discover improved diagnostic techniques and new methods of therapy, management and prevention.

In the past year, Institute investigators have performed numerous fruitful studies on the biochemistry of blood coagulation, with particular emphasis on developing better forms of therapy for various congenital and acquired hemorrhagic ("bleeding") diseases, among them, hemophilia A or B, von Willebrand's disease, and such hemophiloid conditions as Factor V or Factor VII deficiency, circulating anticoagulants, afibrinogenemia, and fibrinolysis. The immunological aspects of thrombocytopenia, anemia, and granulocytopenia also are under investigation, and new approaches to therapy of acute and chronic idiopathic thrombocytopenic purpura (ITP) and of the thrombocytopenia of lupus enythematosus are being evaluated.

Among the more significant studies conducted by Institute scientists in the past year was one which led to the discovery of two previously unknown blood factors which are potent anti-coagulants and which may play a major role in several bleeding disorders. The two factors cause profound bleeding when infused into animals, similar to that seen in patients with the rare blood disorders defibrination or fibrinolysis. This work suggests that these two previously undefined blood factors are the principal causes of hemorrhage in such patients..

The requested increase of $690,000 will provide $525,000 for modest increases in each of the disease areas described above, $42,000 for annualization of ten new positions authorized in 1968, $73,000 for annualization of the 1968 pay increase, $16,000 for one extra day of pay in 1969 and $34,000 for centrally furnished services from the National Institutes of Health management fund.

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 29 | $ 320,000 | 29 | $ 326,000 | | +$ 6,000 |
| Other expenses..... | __ | 7,267,000 | __ | 7,273,000 | | + 6,000 |
| Total..... | 29 | 7,587,000 | 29 | 7,599,000 | | 12,000 |

Introduction

The mission of the Institute and the versatile role it must play in pursuit of its goals have evolved modes of approach to problems which fall within the Institute's province of responsibility which cannot be met through either the intramural or the extramural system, both of which support projects essentially of the competent investigator's own choice. It is not easy to induce scientists to shift from studies in which they are effectually engaged to work on new problems. When Institute staff decide that it is essential to pursue a particular Institute project, and specific talents or resources are not available within the Institute, direct collaboration is sought with the necessary outside talent or resource to further accomplishment of the specific task. Thus, a type of Institute activity has been evolved which is financed by direct operations funds of the Institute and which makes use of the contract mechanism; this is the "collaborative" approach in pursuit of Institute goals.

This area of activities may be referred to as "developmental research" or "programmed research". Involved are usually structured, planned, mission-oriented, purposeful, Institute-directed efforts aimed at the achievement of a definite objective. Their need arises particularly in situations where preceding extensive fundamental laboratory and clinical research has advanced the state of knowledge of a particular field to the point where it is ripe for planned exploitation with specific targets in mind, such as the development of new diagnostic tests or of specific therapeutic modalities--a new vaccine, a new drug, a different approach to organ transplantation, or a new external prosthesis. Traditionally such programmed activities have also included specific activities aimed at providing investigators in a certain field with new tools of the trade, be they highly purified standard chemical substances or biologicals to aid ongoing research, or the development of new and complex laboratory equipment and instruments for the specific solution of a research problem or for use in clinical treatment of patients.

Also grouped in these activities is the important area of scientific communications, which includes the publication of current-awareness journals, the preparation of films and other communications media, and the organization, when needed, of specific scientific working conferences.

Artificial Kidney Program

Background

In the United States today an estimated 50,000 individuals die each year as a result of irreversible kidney failure. The diseases which originally initiate the chain of events which terminates with advanced kidney failure vary considerably in nature. They may be primary kidney diseases like glomerulonephritis. In other instances, progressive kidney damage may be induced by longstanding hypertension or diabetes, or kidney infection and destruction may be initiated by obstructions such as kidney stones or hypertrophy of the prostate in aged males. Regardless of the original disease, the progressive kidney damage leads to a common final pathway, end-stage kidney disease, followed by fatal irreversible kidney failure.

Although artificial kidneys had been known for many years, until 1960 they could only be used a few times in each individual for lack of a practical method for repeatedly connecting the patient's bloodstream with the artificial kidney machine. In that year a group of Institute grantees at the University of Washington developed permanently indwelling plastic blood vessel connections )"cannulas") which made possible the repeated joining of patients with irreversible kidney failure to artificial kidneys for intermittent maintenance treatment. Subsequently, these investigators proved the feasibility of maintaining life in such patients for a number of years with the aid of artificial kidney treatments ("hemodialysis") given twice or three times each week. With increasing experience with this new treatment modality it soon became evident that existing artificial kidneys and dialysis methods were as yet not optimal, that maintenance treatment with artificial kidneys was extremely expensive and not within the reach of most individuals who needed it, and that rehabilitation of patients on chronic dialysis, using present methods and equipment, was not always optimal. It was estimated, based on recent experience, that about 8,000 patients of the yearly 50,000 individuals with end-stage kidney disease would possess the necessary medical and psychological prerequisites necessary for successful long-term dialysis treatment.

The emergence of this new lifesaving treatment encouraged the Congress, in the summer of 1965, to appropriate additional funds to this Institute for the pursuit of a planned and centrally directed program of research and development, utilizing predominantly a direct contract approach, aimed at the development of improved and less expensive dialysis hardware and methodologies and at optimal rehabilitation of chronic dialysis patients.

The Program

The new Artificial Kidney Program was located in the National Institute of Arthritis and Metabolic Diseases (NIAMD), the Institute which has major responsibility for research in urology and renal diseases.

It was considered important to undertake such a program through the utilization of the best possible consultative talent from both outside and within the National Institutes of Health. Accordingly, outstanding authorities active in the field of chronic uremia and hemodialysis have been appointed as consultants. Among them are physicians who have led programs in artificial kidney centers, renal physiologists, physical chemists and membrane specialists, chemical and electronic engineers, and those rare, talented individuals who combine several of the above qualifications. These consultants are assisting in setting the trend of the program and are reviewing the scientific merit and feasibility of contract proposals.

It was also considered important that the program be undertaken in close cooperation with the activities of the Kidney Disease Control Program of the Bureau of Disease Prevention and Environmental Control of the Public Health Service. The latter activity is concerned largely with the actual demonstration of chronic dialysis in a community setting--both in specialized dialysis centers and, where feasible, in the homes of selected patients. Because of their closely interdigitating and interdependent nature both programs are in close and constant communication and work with a high degree of cooperation. There is a constant exchange of essential data between staffs of these programs, with particular emphasis on program planning activities. This close cooperation assures a maximum of benefit and prompt application of research and development advances in the artificial kidney field.

Program Plans

A thorough study of the state of the art made it apparent that no single specific direction could be followed which would exclude others which might be relevant. Several different types of artificial kidneys are in use at the moment, and different methodologies are being advocated by the various workers in the field. Therefore, at this time, a variety of approaches in artificial kidney development are being supported. Once it becomes evident that one or more approaches show greater promise, efforts will be concentrated in these directions.

The following are considered problems of highest priority: 1) improvement of blood cannulas, 2) a search for possibly more suitable dialysis membranes, 3) development of better dialyzer design including disposable dialysis cartridges, 4) a decrease in requirement for expensive professional personnel, 5) acquisition of data which would permit a meaningful comparative evaluation of the effectiveness of the various dialysis methods and equipment currently in use, and 6) avoidance of the undesirable symptoms frequently found in patients maintained by repeated dialysis.

Following the 1965 Congressional appropriation, the Artificial Kidney Program was mounted in record time with the activation of carefully selected research and development contracts. These contracts were placed with universities, nonprofit research laboratories and industrial concerns, and constitute a broad spectrum approach to the problems of highest priority. These projects involve development of improved blood cannulas and filtration membranes; evaluation and development of new polymer surfaces for artificial kidneys, cannulas and membranes which do not induce blood coagulation; design of more efficient, compact, and less costly dialyzer systems; development of a new concept of artificial kidney dialysis ("hollow fiber" or "capillary" kidneys); research on and development of absorption cartridges for blood purification; research on the utilization of ultrasonics to speed up dialysis in artificial kidneys; development of inexpensive disposable dialysis units; improvement and design of new automated centralized artificial kidney systems; improvement and design of new dialysis units with automated fail-safe mechanisms; design and development of prototype for miniaturized or portable artificial kidneys, and many other related projects.

A substantial portion of the new contracts embody unique, new approaches to artificial kidney methodology such as diafiltration; development of new types of permanent arteriovenous shunts; introduction and evaluation of novel materials for cannulas; development of additional types of capillary (hollow fiber) artificial kidneys; evaluation of a special protein restricted diet in the maintenance of uremic patients for whom chronic dialysis is deemed not feasible or unobtainable; isolation from dialysates and identification of the as yet unknown compound(s) which is (are) specifically responsible for the toxic symptomatology in uremia, and many other projects related to improved dialysis methodology or apparatus.

A patient registry coupled with a medical, engineering and economic analysis of all patients on chronic dialysis has been instituted with the Research Triangle Institute as the contractor. The contract provides for a registry of all patients presently maintained with the aid of artificial kidneys or peritoneal dialysis, and will permit a truly comparative evaluation of the effectiveness of the equipment used and of the various methodologies of treatment. The patient registry project aims at a meaningful comparative evaluation of the various facets, steps and methodologies involved in chronic dialysis, from selection of the patient through his medical evaluation once he is being maintained with chronic dialysis. This overall systems analysis will be undertaken as a cooperative effort with the community service programs in dialysis of the Kidney Disease Control Program of the PHS; it will cover the various dialysis centers of the Veterans Administration Hospitals and all other centers or hospitals engaged in chronic dialysis and willing to cooperate.

In addition, there has already been an exchange of information with the personnel involved in the annual dialysis survey of the European Dialysis and Transplant Association concerning information obtained during its annual cross section survey of the patient population in Europe, which equals approximately

the number of patients on dialysis in this country. Since a number of valuable innovations has originated in Europe and since the patient problems are similar, access to the European data and a mutual exchange of information will increase the value of both registries, particularly as to the medical, clinical, and technical aspects of dialysis.

In the process of instituting this registry it has become increasingly apparent that the medical and clinical aspects of chronic dialysis require detailed evaluation, particularly with regard to efficacy in controlling the various symptoms associated with uremia and with regard to the long-term deleterious effects on the nervous system, blood and bones.

The ideal diet for patients in dialysis is still a matter of controversy and disagreement among the experts. Some favor high protein diets with frequent dialyses, whereas others favor special selected low protein diets with infrequent or occasional dialyses. Also, some favor entering patients into dialysis programs on a preventive basis prior to terminal uremia, while the patient still has some kidney function, whereas others adopt the opposite approach and attempt to delay as long as possible the time when dialysis must be instituted. In order to help resolve these matters various centers are being stimulated to study these problems in a detailed and organized way.

A working conference on the dietary management of chronic renal failure, cosponsored by the Artificial Kidney Program of the Institute and the Kidney Disease Control Program, BDPEC, PHS, was held October 2-3, 1967. The two-day session was designed to analyze and communicate certain aspects of current knowledge of dietary therapy in the management of patients with chronic renal failure. Special emphasis was devoted to a comparative evaluation of a new type of diet, developed in Italy and England, which limits dietary nitrogen intake to minimal amounts of essential amino acids, and which has permitted limited survival and rehabilitation, in certain types of patients with chronic renal failure, without recourse to kidney transplantation or artificial kidneys.

As a result of the meeting a number of pertinent clinical studies will be undertaken by several participants, in addition to the work already currently supported by the Program in this area, with special emphasis on the use of variations of this diet coupled with occasional, infrequent dialyses, in many patients who cannot now obtain regular chronic dialysis treatment. The proceedings of the Conference will be published as a special supplement to the monthly American Journal of Clinical Nutrition and copies will be made available subsequently to all workers in the field of chronic renal failure.

As a result of the success of this Conference a similar conference on abnormal calcium metabolism and bone disease in uremia and dialysis patients is planned for the fall of 1968.

In 1967 the Program began publication of the quarterly Artificial Kidney Bibliography. This current-awareness publication provides information on the latest scientific articles published anywhere in the world concerning renal failure, dialysis, artificial kidneys, and kidney transplantation. It is made available, without cost, to NIH grantees engaged in kidney disease research, to contractors of the Artificial Kidney Program and, upon request,

to other qualified interested investigators and practitioners working in areas closely related to the artificial kidney. The laudatory response of the recipients of this new publication has been very gratifying.

The Program has also published and widely distributed the publication A Review of the Development and Performance of Hemodialyzers which was prepared by one of its contractors. Among other essential subject matter it contains tables which, for the first time, compile and compare performance data on the various existing dialyzers and dialysis membranes--an indispensable aid to anybody engaged in artificial kidney improvement.

Accomplishments

In the past year there have been a number of accomplishments and encouraging developments in the research and development contract program. A compact, high-efficiency dialyzer for artificial kidney machines has been developed which permits treatment of almost twice as many patients in a given dialysis center setting as with conventionally used dialyzers. The Babb-Grimsrud (B-G) dialyzer, named for its developers, measures only 20 by 50 centimeters and is constructed of plastic and a commercially available foam nickel support material. It requires a total blood volume of only 70 cc., thus decreasing the presently high blood priming requirement and the need for compensatory blood transfusions. It costs half as much as the conventionally used two-layer Kiil dialyzer, can be assembled in ten minutes and can be sterilized in an autoclave. Compared to the Kiil dialyzer, the B-G dialyzer has approximately one-third the membrane area, one-seventh the blood volume, and one-fourth the weight, with no decrease in urea clearance and only slight decreases in creatinine clearance. At the present time a series of these new dialyzers is being built for extensive testing under routine operating conditions.

The same clinicians involved in collaborating with the engineers on the Babb-Grimsrud dialyzer design at the University of Washington, Seattle, have devised a technique for storing and re-using artificial kidneys of the Kiil type and of the attached blood tubing, which reduces the cost and simplifies the work involved in performing hemodialysis in the home. The new procedure permits re-use of the artificial kidneys for at least three successive dialyses, requires assembling and disassembling of the unit only once instead of three times a week, and allows use of blood tubing sets at least nine times, for an estimated saving of $900.00 per year. The clinicians involved in developing this are involved also in other contracts of research and development in the dialysis area.

The new and unique hollow fiber capillary kidney, which is being developed under a contract with the Dow Chemical Company, is progressing according to schedule and has already been tried on one patient. A semi-automated facility has been set up under the contract in order to expand the production of prototype models which will be put into clinical testing shortly. The advantage of this design is that it is compact, disposable, and as efficient as dialyzers in current use, and lends itself to mass production. The design consists of small bundles of many hollow cellulosic

fibers through which the blood is passed and which are washed by a blood-purifying dialyzing solution. In addition to the above-mentioned two new artificial kidney designs, other possible designs are being explored including other approaches to the hollow fiber dialyzer design.

Another contractor who is manufacturing the conventional Kiil dialyzer has been successful in the development of a new type of multiple minute pyramidal membrane supports which increase the effective dialysis area of the membrane in the Kiil dialyzer. Preliminary laboratory tests have shown that this new development has increased the dialyzing efficiency of these modified Kiil dialyzers by about 40%. A series of the new type of dialyzer is now being built for clinical testing with patients.

The activities of the Program have also resulted in an increase, in this country, in the use of a new type of diet, developed in Italy and England and heretofore used primarily abroad, which has permitted limited survival and definite rehabilitation in certain types of patients with chronic renal failure, where recourse to kidney transplantation or artificial kidneys is not possible or advisable.

Current Plans

The Program will continue all promising current research and development efforts and will pursue any new ideas and approaches which appear feasible. Among these is a new method of detoxification of uremic blood with the aid of special selective adsorbing agents (in contrast to the presently used purification with the aid of membrane dialysis). The complete success of such detoxification-by-adsorption hinges on the successful identification of all toxic substances which accumulate in the bloodstream in kidney failure. The Program is currently funding a number of studies aimed at the isolation and identification of such unknown toxic factors which may have to be removed from the patients' blood, in addition to metabolic wastes and other substances known to accumulate during kidney failure, such as urea, creatinine, uric acid, potassium, hydrogen ion, and water.

The Program will support further development of special diets (see above) for maintenance of uremic patients, to be used in conjunction with infrequent peritoneal dialysis or hemodialysis. For the latter type of regimen patients would be given surgically constructed, subcutaneous, natural arterio-venous blood vessel shunts (which are very adequate for infrequently administered hemodialysis). It is hoped that with the aid of such a special diet-infrequent-dialysis regimen patients would be maintained without the need for implantation of plastic shunts, and that a larger number of patients with renal failure may be accorded life-saving treatment in this fashion in the face of the great expense of conventional chronic dialysis therapy which is unavailable to most patients with end-stage kidney disease.

Scientific Communications

A continuing problem confronting individual physicians and research scientists today is keeping abreast of current developments and advances in their respective areas of interest or field of work. To meet this communications gap, this Institute initiated several years ago a major program of monthly current-awareness publications in its principal fields of responsibility, designed to make available in concise form to interested physicians and scientists abstracts, citations and bibliographies of all current scientific papers and literature most relevant to their particular spheres of interest, which ave been published within recent weeks or months anywhere in the world and in any language.

The enthusiasm with which these publications were received and their acceptance and wide use by the scientific community more than bears out the need for such publications. Among the current-awareness journals now successfully meeting this challenge are Arthritis and Rheumatic Diseases Abstracts, Gastroenterology Abstracts and Citations, Diabetes Literature Index, and Artificial Kidney Bibliography. The three journals are expected to continue in the next year in much the same form. As a result of the Institute's experience and of responses from recipients, Artificial Kidney Bibliography, will see a needed change. Henceforth, this quarterly publication will appear on a monthly basis and a quarterly abstract publication will be added to this monthly bibliography. These changes are expected to permit more effective coverage of the latest developments and advances, as described in the world literature, in artificial kidney apparatus and technology, clinical dialysis methodology, kidney transplantation and fundamental and clinical knowledge concerning chronic kidney failure.

In the past year, a prototype of a new current-awareness journal has been developed in the field of endocrinology, to be known as the Endocrinology Index. At present, two experimental issues have been compiled for a limited distribution to interested professionals in the field, to evaluate the usefulness and format of this type of journal. It is expected that Endocrinology Index will cover the entire field of endocrinology, excepting pancreatic function (which is covered in Diabetes Literature Index), with regular publication hoped for in 1968.

The Institute, in collaboration with the National Institute of Child Health and Human Development, is engaged in the development of another journal to fill the existing communications gap in the field of nutrition.

In the past year, the Institute's Office of Scientific Communications in cooperation with the National Cystic Fibrosis Research Foundation produced a 16 mm. color medical teaching film, "Diagnosis and Management of Cystic Fibrosis", intended for physicians, medical students, nurses, physical therapists and other professionally concerned with this inborn metabolic disorder. The film has been received enthusiastically and will be made widely available through both sponsoring agencies.

National Pituitary Agency

In December 1967 the NIAMD awarded a new contract in the amount of $287,500 to the University of Maryland School of Medicine to continue through the National Pituitary Agency the collection of human pituitary glands and the preparation distribution of human growth hormone (HGH) for research and clinical studies on problems of human growth by qualified investigators. Insufficient secretion of HGH by the pituitary gland results in a condition called hypopituitary dwarfism, treatable by administration of additional HGH.

Currently the main problem facing fundamental and clinical research related to HGH is the scarcity of the hormone, available presently only from the pituitary glands of the deceased. Research has shown that one human pituitary gland provides only enough HGH for about five days of treatment of a hypopituitary child. Unfortunately, extracts of growth hormone from animal pituitary glands have not proved active in man.

In an effort to alleviate the problem, the NPA is seeking to increase and improve collection of human pituitary glands and to provide for the distribution of purified HGH to qualified research scientists.

Extramural clinical studies are designed to determine HGH's metabolic effects and mechanism of action. Other biochemical studies are designed to elicit the molecular structure of HGH in order to make possible its laboratory synthesis and to eliminate reliance on the natural hormone. Presently, HGH can be administered only to patients in conjunction with clinical studies since it is not possible to collect enough human pituitary glands to obtain sufficient HGH for treating the estimated 5,000-10,000 children suffering from hypopituitary dwarfism in this country. To aid as many as possible, the NPA's Medical Advisory Board review applications submitted by research endocrinologists and determines the scientific merit of the proposals and the amount of hormone each investigator is to receive based upon the requirements of each proposed study and the available supply. Under this research program, about 400 children with various problems of growth are currently being given HGH in clinical studies.

In this connection, a scientist at the University of California at Berkeley who has received HGH from the NPA and whose research is supported by this Institute, recently identified the chemical structure of this hormone, a finding that marks a major advance in understanding of the several modes of action of HGH and increases chances for its eventual synthesis. Meanwhile, other studies using HGH from the agency are attempting to modify chemically HGH from cattle to make it biologically effective in man. These scientists, at New York's Memorial Sloan-Kettering Cancer Center, whose research also is supported by the NIAMD, have demonstrated that bovine growth hormone modified by digestion with the enzyme trypsin elicits in man many of the characteristic metabolic responses of human growth hormone.

The increase in this activity will provide $6,000 for annualization of the 1968 pay increase and $6,000 for centrally furnished services from the National Institutes of Health management fund.

Biometry, Epidemiology and Field Studies

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 27 | $196,000 | 27 | $203,000 | | +$7,000 |
| Other expenses..... | | 517,000 | | 518,000 | | +1,000 |
| Total..... | 27 | 713,000 | 27 | 721,000 | | +8,000 |

Epidemiology research is recognized today as a science indispensable to the advance of biomedical knowledge. The Institute's Clinical Field Studies Unit has in a comparatively short time amply demonstrated the value and importance of research of an epidemiological and clinical nature. Investigators of this Unit are actively studying the genetic and environmental factors related to the occurrence of clinical diabetes and its complications and are evaluating possible therapeutic or preventive measures. A survey by this Unit, for example, demonstrated that the Pima Indians have by far the highest prevalence of diabetes ever reported in any population group.

Based in Phoenix, Arizona, the Unit now conducts its research studies at the portable clinical facility attached to the DIH hospital on the Pima Indian Reservation at Sacaton, about 40 miles south of Phoenix. So fruitful have the Pimas proved as research subjects that the Unit, in addition to continuing its studies in arthritis and diabetes, has expanded research activities to include the field of gastroenterology, specifically liver and gallbladder disease.

The original epidemiological study among more than 1100 Pima Indians in which a diagnosis of diabetes was made revealed a high prevalence of diabetes with a significant excess in each decade in females aged 45 years or over. In the past year, clinical investigators of this Unit have shown that the effects of childbearing do not account for the higher prevalence of diabetes among women. Of about 700 females studied, over half had borne four or more children and one-fifth had borne seven or more children. Since the Pimas have large families in addition to a high prevalence of diabetes, the data was analyzed to test the hypothesis that increasing parity is associated with an increased risk of diabetes. In spite of a high prevalence of diabetes and the frequent occurrence of large families, no evidence of any relation between increasing parity and the age specific prevalence of diabetes was found. Nor was the prevalence of diabetes in women aged 45 years and over who had borne seven or more children greater than in women who had borne none. Contrary to expectations, the prevalence of diabetes, especially in the younger age groups, was found somewhat higher in those Indian females who have borne no children than in those who have borne seven and more children.

Another significant study by this Unit this past year revealed an unusually high prevalence of gallbladder disease in this population. Studies are underway to document further the prevalence of gallbladder disease in the Pima Indians, to investigate associations between gallbladder disease and possible predisposing factors in this population, and to compare the gallbladder disease prevalence in this circumscribed population with that of the predominantly Caucasian community of Framingham, Massachusetts.

More recently information was compiled which showed that the Pima Indians also have a rate of gallbladder disease that is six times higher than that found in a similar gallbladder study done among Caucasians in Framingham, Massachusetts. Although no association could be found between diabetes and gallbladder disease in Pima females, 80 percent of Pima men over 45 with gallbladder disease also had diabetes. Precisely what influence this finding may have upon ongoing diabetes studies remains to be determined.

Another Unit of the Institute's Epidemiology and Field Studies Branch conducts iodine metabolism field studies, the long-term objectives of which are to examine closely the principal environmental factors associated with the prevalence of goiter and to study the nature of the metabolic defect responsible for this disorder. This study is part of an overall effort aimed at finding better means of preventing goiter and hyperthyroidism. The program includes field studies of water supplies in areas where goiter is endemic, are carried out in Virginia in collaboration with State and local health departments to determine the principal anaerobic bacterial flora of the local water supply; experimental studies in animals in collaboration with the Institute's Laboratory of Nutrition and Endocrinology, to determine if changes in the intestinal flora of rats influences their thyroid status; and clinical studies in collaboration with the Institute's Clinical Endocrinology Branch involving qualitative and quantitative studies of the human fecal flora in normal control subjects, hyperthyroid subjects and one euthyroid patient.

The increase in this activity will provide $4,000 for annualization of two new positions authorized in 1968, $2,000 for annualization of the 1968 pay increase, $1,000 for one extra day of pay in 1969 and $1,000 for centrally furnished services from the National Institutes of Health management fund.

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 80 | $742,000 | 85 | $791,000 | +5 | +$49,000 |
| Other expenses..... | | 1,505,000 | | 1,520,000 | | +15,000 |
| Total..... | 80 | 2,247,000 | 85 | 2,311,000 | +5 | +64,000 |

Introduction

This activity is composed of professional and supporting personnel who are responsible for the administration of the Institute's several grants activities. This involves 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 PHS, advisory bodies, and interested organizations, continuous surveillance of scientific activities and progress; and recording and reporting of fiscal and scientific information relevant to all transactions.

The increase requested will provide five new positions and $30,000 for additional grants management and professional analysis staff needed to administer the complex problems presented by the growing number of competitive grant applications and the rising cost of biomedical research. This increase will enable the staff to take the many complex administrative actions to negotiate the minimum obligation for each grant, thereby increasing the total number of grants, fellowships and training grants which can be awarded from the funds appropriated.

The increase will also provide $5,000 for annualization of two new positions in 1968, $11,000 for annualization of the 1968 pay increase, $3,000 for one extra day of pay in 1969 and $15,000 for centrally furnished services from the National Institutes of Health management fund.

Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 23 | $227,000 | 25 | $260,000 | +2 | +$33,000 |
| Other expenses | | 144,000 | | 164,000 | | +20,000 |
| Total | 23 | 371,000 | 25 | 424,000 | +2 | +53,000 |

This activity is comprised of the Institute Director, his immediate staff and administrative management and service personnel who are responsible for the general direction, coordination and administration of the total Institute activities.

The requested increase will provide two positions and $20,000 for specialized professional assistance to the Institute Director and to provide for in-depth studies relating to the programming and budgeting systems in the Institute. The request also includes $9,000 for annualization of three new positions authorized in 1968, $3,000 for annualization of the 1968 pay increase, $1,000 for one extra day of pay in 1969, and $20,000 for centrally furnished services from the National Institutes of Health management fund.

WEDNESDAY, MARCH 20, 1968.

# NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

## WITNESSES

DR. RICHARD L. MASLAND, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ELDON L. EAGLES, ASSISTANT DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
ECKART WIPF, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
ROBERT L. SITHENS, BUDGET OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 5,961 | 7,074 | 7,496 |
| Positions other than permanent | 244 | 263 | 278 |
| Other personnel compensation | 81 | 88 | 92 |
| Total personnel compensation | 6,286 | 7,425 | 7,866 |
| Personnel benefits | 619 | 717 | 740 |
| Travel and transportation of persons | 389 | 453 | 560 |
| Transportation of things | 77 | 80 | 109 |
| Rent, communications, and utilities | 213 | 220 | 250 |
| Printing and reproduction | 36 | 50 | 80 |
| Other services | 678 | 737 | 775 |
| Project contracts | 3,657 | 9,050 | 9,235 |
| Payments to "National Institutes of Health management fund" | 5,428 | 6,106 | 6,413 |
| Supplies and materials | 1,082 | 1,085 | 1,090 |
| Equipment | 919 | 700 | 890 |
| Grants, subsidies, and contributions | 93,125 | 99,931 | 103,189 |
| Insurance claims and indemnities | 2 | | |
| Subtotal | 112,511 | 126,554 | 131,197 |
| Quarters and subsistence charges | −2 | −2 | −2 |
| Total obligations | 112,509 | 126,552 | 131,195 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 776 | 793 | 830 |
| Full-time equivalent of other positions | 45 | 60 | 60 |
| Average number of all employees | 729 | 801 | 850 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 71,177 | 77,346 | 80,038 |
| (b) Fellowships | 3,434 | 3,805 | 3,889 |
| (c) Training | 18,514 | 18,780 | 19,262 |
| Total, grants | 93,125 | 99,931 | 103,189 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 8,473 | 9,894 | 11,119 |
| (b) Collaborative research and development | 4,264 | 10,190 | 10,206 |
| (c) Biometry, epidemiology, and field studies | 2,193 | 3,371 | 3,388 |
| (d) Training activities | 69 | 73 | 74 |
| (e) Review and approval of grants | 2,054 | 2,418 | 2,499 |
| (f) Program direction | 731 | 675 | 720 |
| Total, direct operations | 17,784 | 26,621 | 28,006 |
| Total program costs, funded [1] | 110,909 | 126,552 | 131,195 |
| Change in selected resources [2] | 1,600 | | |
| Total obligations | 112,509 | 126,552 | 131,195 |
| Financing: | | | |
| Comparative transfers to other accounts | 558 | | |
| Unobligated balance lapsing | 3,217 | 404 | |
| New obligational authority | 116,284 | 126,956 | 131,195 |
| New obligational authority: | | | |
| Appropriation | 116,296 | 128,633 | 131,195 |
| Transferred to other accounts | −12 | | |
| Appropriation (adjusted) | 116,284 | 128,633 | 131,195 |
| Proposed transfer to other accounts for pay increases | | −1,677 | |
| Relation of obligations to expenditures: | | | |
| Total obligations | 112,509 | 126,552 | 131,195 |
| Receipts and other offsets (items 11–17) | 558 | | |
| Obligations affecting expenditures | 113,067 | 126,552 | 131,195 |
| Obligated balance, start of year | 64,824 | 71,244 | 90,467 |
| Obligated balance, end of year | −71,244 | −90,467 | −110,962 |
| Adjustments in expired accounts | −3,700 | | |
| Expenditures | 102,947 | 107,329 | 110,700 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 46,813 | 48,806 | 46,700 |
| Out of prior authorizations | 56,134 | 58,523 | 64,000 |

[1] Includes capital outlay as follows: 1967, $609,000; 1968, $700,000; 1969, $890,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $1,790,000; 1967, $3,390,000; 1968, $3,390,000; 1969, $3,390,000.

Mr. FLOOD. We now have the National Institute of Neurological Diseases and Blindness. The presentation will be made by Dr. Richard L. Masland, who is the Director.

We have a biographical sketch of Dr. Masland which we will put in the record.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

(The sketch follows:)

BIOGRAPHICAL SKETCH

Name: Richard L. Masland, M.D.

Position: Director, National Institute of Neurological Diseases and Blindness (NINDB).

Birthplace and date: Philadelphia, Pa., March 24, 1910.

Education: A.B., Haverford College, 1931; M.D., University of Pennsylvania School of Medicine, 1935 (Diplomate, Am. Bd. of Neurology and Psychiatry—Neurology 1943, Psychiatry, 1948).

Experience: 1959—Director, NINDB; 1957–9 Assistant Director, NINDB; 1955–57 Professor, Psychiatry and Neurology (neurology); Associate in Physi-

ology, Bowman Gray School of Medicine; 1955–56 On leave of absence, Research Director, National Association for Retarded Children; 1948–55 Associate professor, Psychiatry and Neurology (neurology) and Assistant Professor of Physiology, Bowman Gray School of Medicine; 1947–48 Assistant Professor, Psychiatry and Neurology (neurology) Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N.C.; 1946 Fellow in Psychiatry, Pennsylvania Institute for Mental Hygiene; 1943–45 U.S. Army, Director, Department of Physiology, School of Aviation Medicine, Randolph Field, Tex.; 1940–46 Associate in Neurology, University of Pennsylvania; 1939–46 Assistant Neurologist, Pennsylvania Hospital; 1938 Fellow in Neurology, University of Pennsylvania; 1935–37 Intern, Pennsylvania Hospital, Philadelphia.

Association memberships: American Academy of Neurology; American Association of Neurological Surgeons; American EEG Society; American Epilepsy Society; American Neurological Association; Association for Research in Nervous and Mental Disease; Association for Research in Ophthalmology; Eastern EEG Society; Myasthenia Gravis Fund; North Carolina Neuropsychiatric Association; Philadelphia County Medical Society; National MS Society Medical Advisory Bd; Res. to Prevent Blindness, Scientific Advisory Panel; Roscoe B. Jackson Mem. Lab. Bd. of Scientific Overseers; UCP Res. and Educa. Fnd. Research Advisory Com; Muscular Dystrophy Assoc. of America Med. Adv. Bd; Jos. P. Kennedy Jr. Fnd. Scientific Advisory Bd; Montg. Co. Med. Soc. and Md. State Med. and Chirurgical Faculty; American Public Health Assoc; VA. Adv. Com. to P&N Service; American Heart Assoc. Coordinating Com. in Nationwide Stroke Program.

Special awards, citations or publications: Alpha Omega Alpha, 1934; Phi Beta Kappa, 1941; Sigma Xi, 1956; National Tay-Sachs Association Annual Award, 1961; National Assoc. for Retarded Children, 1963; National Multiple Sclerosis Society's Bronze Chest Award, 1964; Myopia Research Fnd. Award, 1964; N.Y. State Assoc. for Retarded Children, Inc., 1965; United Cerebral Palsy Assoc., Max Weinstein Award, 1967; DHEW Superior Service Award, 1967; American Speech and Hearing Assoc., Honors Award, 1967.

## General Statement

Dr. Masland. Mr. Chairman and members of the committee, it is my privilege to appear before you in behalf of the National Institute of Neurological Diseases and Blindness, created by act of Congress in 1950.

### AREAS OF SERIOUS CONCERN

As reflected in the President's state of the Union message, we have a serious concern for the health of two groups of our citizens—the very young and the over 65-age group. Neurological and sensory disorders represent a major cause of disability among these segments of our population. For the very young, these diseases include cerebral palsy, epilepsy, and sensory disorders, particularly disorders of language. For the over 65-age group, stroke, Parkinsonism, and the sensory disorders, particularly blindness, are high on the list. For the in-between age groups we have concern for the neuromuscular and sclerosing disorders, and for all age groups, brain tumors, and both head and spinal cord injuries.

Because of research accomplishments of the past 20 years, many of these disorders can now be prevented and others can be effectively treated if diagnosed early. Increasing knowledge in the perinatal field is saving children from a lifetime of disability. Increasing numbers of our senior citizens can now live useful, well-adjusted lives rather than face the prison of the paralyzed, the silent isolation of the deaf, or the never-ending night of the blind.

In spite of these advances, thousands of Americans still are developing neurological and sensory disorders for which the cause is unknown

and no effective treatment is available. I should like to refer especially to several areas of great national need toward which the Institute desires to focus an increasing allocation of the resources made available to us.

### COLLABORATIVE PERINATAL PROJECT

The Institute's collaborative perinatal project, which has been underway since 1959, is proceeding on schedule and is now concentrating increasing emphasis on the interpretation of the accumulated data. Only the most preliminary analyses are yet available but already many new facts are emerging and other long suspected factors are being confirmed. Premature children have been shown to have a high percentage of neurological abnormalities, and birth weight has shown itself to be the best predictor of the child's chance for survival after birth. New knowledge has been gained on the relationship of unfavorable pregnancy outcome to such factors as nutrition, maternal age, metabolic imbalance, toxins, and radiation. And much more is now known about infections during pregnancy.

### HEAD INJURY

Recently the Nation has become aware of the tremendous loss of life and productivity from accidents involving head injury. Four medical centers now have Institute grants to establish head injury clinical research centers, and several other centers are ready to participate. The Institute also has a contract program studying the physical effects of various forms of head injury. The extent and causes of the problem are the subject of a scientific survey.

### EPILEPSY

Epilepsy receives a major emphasis of the Institute's research program. The Institute is now supporting four clinical epilepsy research centers. Additionally, a group of four collaborating units are studying the methodology for the evaluation of various epileptic states and the testing of drugs for the control of epilepsy. An abstract service is bringing the newest advances promptly to the attention of the scientific community.

### STUDIES OF MOVEMENT AND SENSATION

Last year the Institute launched a program for the study of control of movement and sensation in the normal and the neurologically paralyzed. All feeling, thought, and movement depend upon nerve activity—activity now capable of being recorded by advanced eletronic equipment and analyzed by computers. Full understanding of the functions of sensation, hearing and vision, and the control of voluntary movement requires an intimate knowledge of the neural processes which underlie these functions. With such knowledge it may ultimately be possible to bypass or replace damaged organs for hearing or sight, or to compensate for disorders in the control of voluntary movement. Conceivably, for certain types of man-machine

interaction, direct contact of machine to nervous system might be effective. The Institute is now exploring these possibilities in a broad new approach to the study of neurological control processes.

VIRUSES

The causes of multiple sclerosis, parkinsonism, and amyotrophic lateral sclerosis continue to remain an enigma. Lacking an understanding of the causes, the treatment of these disorders is distressingly futile. New discoveries regarding the role of viruses in brain diseases suggest the possibility that these agents may be responsible for many chronic disorders previously spoken of merely as "degenerative."

The Institute has mounted a major program for the study of viruses. Their sinister nature requires that a specially designed facility be made available to provide a safe environment for the dedicated scientists devoted to such studies. Included in the PHS construction appropriation are planning funds for such a building. Within our present facility, we plan to continue an active program in this field.

SUMMARY OF 1969 BUDGET REQUEST

The request for the National Institute of Neurological Diseases and Blindness for 1969 is $131,195,000, compared to he 1968 operating level of $126,552,000. The 1969 budget request contains increases of $4,643,000 including: $2,692,000 for research grants; $84,000 for research fellowships; $482,000 for training grants; $1,225,000 for laboratory and clinical research; $16,000 for collaborative research and development; $17,000 for biometry, epidemiology, and field studies; $1,000 for direct training; $81,000 for review and approval of grants; and $45,000 for program direction.

I shall be happy to answer any questions.

Mr. FLOOD. As you say, your budget for 1968 is for $126,552,000; you are asking for $131,195,000 in 1969.

Dr. Masland, that is an increase of $4,643,000. But for all practical purposes this request is for only enough to keep you at the current level, it would seem, for your grant programs, and most of your direct operations. Is that about it?

Dr. MASLAND. Yes, sir. Within the direct operations we just completed our new laboratory building, which has been under construction now for 6 or 7 years. There are increases in our direct operations to make it possible for us to man and equip that new building.

PERSONNEL INCREASE

Mr. FLOOD. You have an increase of 30 positions in the laboratory and clinical research, and you have seven for review and approval of grants. Why are they necessary?

Dr. MASLAND. Those 30 positions are specifically for the new laboratories which will become available starting in July of this year.

Mr. FLOOD. Separate from review and approval of grants?

Dr. MASLAND. Yes. The seven for renewal and approval of grants reflect an increase of fiscal management and the necessity for us to maintain a very precise overview of the program.

HEAD INJURIES

Mr. FLOOD. You will recall that last year the committee suggested in its report that you give attention to problems arising from head injuries.

Dr. MASLAND. Yes, sir.

Mr. FLOOD. You mentioned this in your affirmative statement. How did you suddenly come to discover the dramatic statistics on head injuries?

Dr. MASLAND. Mr. Chairman, our planning for a program on head injuries actually was launched as early as 1965 when members of the staff became aware of the fact that this was an area of the institute's activities that was not being developed in proportion to the size of the problem.

Mr. FLOOD. How is it that the Nation has suddenly awakened to the fact that it has a substantial and serious problem with head injuries? Why wasn't this problem uncovered yesterday or 10 years ago? Why today?

Dr. MASLAND. This is one of the types of questions which is reviewed by the Council periodically. Increasingly within the institute we have been developing a program analysis activity whose role it is to assess the national need in various areas, and to review the total institute program.

You raised the question a few moments ago regarding the seven additional positions in review and approval. One of the types of activities those added people are to be engaged in is the scientific analysis of our program from the point of view of national need, and the relationship and effectiveness of our research relative to it.

Mr. FLOOD. I am sure of that Doctor. But I can never understand why somebody has not been worried about that before this. Did you not have statistics on it?

Dr. MASLAND. You must recall that the Institute was established a little more than 10 years ago. The development of our organization for conducting this type of analysis is relatively new, within the last 5 or 6 years. The statistics on medical problems are still relatively inadequate and one of the important tasks included in many of our program areas is that of obtaining more precise figures regarding the incidence of neurological and sensory disease.

Until 5 or 6 years ago, the Institute relied very heavily upon the initiative and the planning of the individual scientist in his decisions as to where the research opportunities lay. We still rely very heavily on this method of determining priorities, and I believe that we should. Through this mechanism, program emphasis represents the sum of the individual thinking of a large number of people. Additionally, we feel that we have the obligation to superimpose upon that a very careful structure of planning and analysis activity.

Dr. SHANNON. When I was testifying as the principal witness last Thursday and Friday, we discussed the development of the total budget of NIH since the summer of 1955. The initial period of about 8 years was a period of what I would call unpressured growth. The need was for scientists-in-being in support of the things they wished to do.

Beginning about 1963, we began a very orderly examination of all programs to find out where were the areas of deficiency in the program when the program was viewed nationally?

Out of this came the program analysis and program planning that led to the identification of many areas of research that are amenable to an organized approach—superimposed upon the general scientific consensus of the nation. The head injuries program falls in that general category.

Actually, this program, as I recall, was really started about 4 or 5 years ago, first by collecting the information that was available. This led to a series of conferences by the Society of Neurological Surgeons, the American Neurological Association, the American Physiological Society, and NINDB which, in turn, led to a study in depth not only of what the problem was—I think we knew what the problem was—but to determine the options available that warranted study.

In other words, Where were the deficiencies in our knowledge? Where was our knowledge solid? And where did we think we could move forward?

At the completion of that study, we immediately saw some fairly obvious investigations that did warrant the type of systematic study that could only be done in an association with very large casualty rates—in the civilian population in relation to highway, industrial accidents and the like, and, indeed in the military, in relation to battlefield casualties.

As a result of the preliminary analysis, the planning and study of the Commission I guess——

Dr. MASLAND. A subcommittee of the Council established a special task force.

Dr. SHANNON. It takes the better part of a 4-year cycle really to mount a program of any significance. I think that you would find that this goes back to a beginning in about the spring of 1964.

### COLLABORATIVE PERINATAL PROJECT

Mr. FLOOD. Now you mentioned the collaborative perinatal project. That is about 10 years old.

Dr. MASLAND. That is correct.

Mr. FLOOD. You should be getting information of some value regularly on that. Do you have anything worthwhile to report in developments during the last year?

Dr. MASLAND. Yes. We are now in the midst of an analysis of these data, although you must recognize that the children are still at a relatively young age and that the analysis of the data cannot be completed until the children reach at least 8 years of age.

It takes a certain period of time for a child to develop before the study can measure its progress. However, all of the more than 50,000 children have been born; the youngest are now approximately 2 years of age. So we are in a position to conduct some analyses from the neonatal period. Some very interesting observations are developing, mainly in terms of quantifying the role and the importance of types of problems which have been previously known to exist. For example, we know now that a woman who has had a certain number of previous unfavorable pregnancies has many times as great a risk for the current

pregnancy. We know that young women, women particularly in the 14- and 15-year age group, have a very unfavorable pregnancy outcome.

We know that women over 40 have, similarily, a very unfavorable pregnancy outcome.

Some very interesting observations now relate to weight change during pregnancy. We have tended to restrict the weight gains of women, and in certain instances this is probably wise. But our studies appear to indicate that there is a very direct relationship between weight gains in pregnancy and the weight and health of the child. Particularly when you have an underweight woman who has a very modest weight gain, the pregnancy outcome is very unfavorable.

We have known for many years that the outcome of pregnancy of diabetic women was unfavorable. From our study, however, we have a strong indication that when diabetes is adequately controlled, so no acidosis occurs, the outcome is not much different than it is for other women. The suggestion is that it is the acidosis which is harmful to the children rather than the diabetes *per se*.

We have a suggestion that albumen loss during pregnancy has an unfavorable outcome. We also have figures and data on the impact of toxemia of pregnancy and hypertension, and the relationship between hypertension and albumen in the urine. These are often related and are being further explored.

We also have some preliminary analyses of drug effects. Here I wish to speak with great caution because these studies are preliminary. However, there are some interesting observations of tetraclycine, which has been given to a certain number of women of this study during pregnancy. Interestingly enough, when moderate doses of tetracycline were given the child seemed to be more healthy than in the case of the controls, on a statistical basis. With large doses, however, there is a suggestion that the IQ of the children, when tested at the age of 4 years, is lower than those born to a group of matched women who did not receive this drug.

Now it is possible that this may have been the harmful effect of the disease for which the tetracycline was given. However, these children had staining of the teeth, which is an effect of the drug. We do have to concern ourselves with whether this was an effect of large drug dosage.

Mr. FLOOD. Now, under what conditions and who decides when a pregnant woman is in the control group? We cannot forget we are talking about the effects upon her unborn child.

Dr. MASLAND. These decisions were made by the physician responsible for the patient's care. I would like to emphasize that this study is purely an observational study and does not constitute an experiment. The whole philosophy and the whole approach of this study has been to observe, but not modify.

From the scientific point of view, this is a weakness.

### EFFECTS OF TETRACYCLINE

Let us take the case of tetracycline——

Mr. FLOOD. I am not speaking from the scientist's point of view.

Dr. MASLAND. But consider it from this angle: in the case of tetra-

cycline we have merely observed the effect of this drug when it was prescribed by the physician in response to his evaluation of the therapeutic needs of the patient. We cannot tell then, without a very sophisticated statistical analysis, whether the unfavorable effect resulted from the drug or resulted from the disease for which the drug was given. In order to determine this with precision, a controlled study must be conducted where some patients are given the drug and some are not. We have not attempted that within the collaborative project's human population.

However, we have established a laboratory for monkeys in Puerto Rico to conduct this type of experiment which we cannot do in the human.

FACILITY IN PUERTO RICO

Mr. FLOOD. I was going to ask you about Puerto Rico with regard to the research you are carrying on there and with regard to the construction of facilities which is so behind schedule.

Dr. MASLAND. The present expectation is that the new laboratory at the Centro Medico will be completed in July of 1970. Things appear to be progressing in an orderly fashion.

We also have temporary construction of animal holding space, another part of that total operation, which is scheduled for March in 1969.

AMYOTROPHIC LATERAL SCLEROSIS

Mr. FLOOD. Many Members of Congress have received a very touching letter from a former Member of Congress on amyotrophic lateral sclerosis. A number of Members have mentioned the contents of that letter to me and have inquired about what this is, giving the impression that this is something that we knew nothing about, and apparently had not been doing anything about. For how long have we actually been doing something about this and to what extent?

Dr. MASLAND. Mr. Flood, if I might say so, amyotrophic lateral sclerosis is an old enemy of mine.

Mr. FLOOD. And a deadly enemy?

Dr. MASLAND. And a deadly enemy. Every medical student in the course of his training thinks he has at least one disease, and amyotrophic lateral sclerosis was the disease that I thought I had. I had twitching of the calf muscles, which is one of the earliest signs of amyotrophic lateral sclerosis. This is sort of a flickering of muscles.

So my first research in 1939 had to do with the twitching of muscles in amyotrophic lateral sclerosis, which I thought might provide a clue to the cause of this disease. I obtained some interesting information about the twitching of muscles, but not about the cause of amyotrophic lateral sclerosis. It was this type of problem which really brought me into the National Institutes of Health. As a practicing neurologist for 10 or 15 years, I was tired of trying to treat people with such diseases, for whom we had no treatment.

In regard to amyotrophic lateral sclerosis, around 1955 it was discovered that this disease is a hundred times as prevalent on Guam as it is in this country, and this seemed to offer a lead—what is different on Guam than exists here?

Mr. FLOOD. You have had a team on Guam for several years.

Dr. MASLAND. We have had a team on Guam since before I came to the Institute, dedicated to a study of amyotrophic lateral sclerosis. They have investigated the food of the inhabitants. We became interested in a toxic nut that the people there use for food, thinking that this might be responsible. And it might give us a clue to some chemical or toxic effect in amyotrophic lateral sclerosis. That lead did not pan out.

We thought it might be a genetically determined disease, and probably in a very small proportion of cases it is. On Guam it appeared to be occurring only in the Chamorro race, but now we find members of other races who live on Guam who have the type of amyotrophic lateral sclerosis which is common there. So evidently it is not a racial problem.

We are doing a followup of Chamorrons who have moved to California, in order to see whether they continue to have this unusually high incidence of the disease within that new environment, hoping again that this will give us a clue as to what factor on Guam is responsible.

About 3 years ago, we assembled members of our own staff at Bethesda to conduct an exhaustive review of the worldwide research effort in amyotrophic lateral sclerosis in order to be absolutely certain that no lead was overlooked. Since that time they have been investigating many patients with that disease, looking for abnormalities of the chemistry of the body which might provide some clue. In addition, they have attempted on an empirical basis a trial of a great variety of forms of treatment—drugs which affect metaboilsm, fat substances, vitamins, nutritional changes. It has been a very broad scale program conducted in our laboratory at Bethesda.

Mr. FLOOD. The committee can say with assurance then that the Institute has been aware of this very dangerous killer for many years.

Dr. MASLAND. Yes.

Mr. FLOOD. And I gather that at NIH there has been a very extensive examination of this disease?

Dr. MASLAND. There is one other effort we have made. About 5 years ago word came to us that the Russians had isolated a virus in this disease. We sent a six-man team to Russia and they had very fine cooperation from the Russian scientists. They were given material and cultures which they brought home for study. However, they were not able to establish a relationship between a virus and A.L.S.

### DISEASES RELATED TO A.L.S.

However, we have established in the neighborhood of Bethesda a very important laboratory where we are now attempting to culture viruses from several similar diseases. Amyotrophic lateral sclerosis, multiple sclerosis, Parkinsonism.

Mr. FLOOD. What is the relationship between those three?

Dr. MASLAND. The relationship is that each involves a slow and progressive degeneration of the nervous system. Certain structures within the brain and spinal cord seem to be selectively destroyed by this disease.

Mr. FLOOD. Speaking of the three?

Dr. MASLAND. Yes. It is a different process. It is a different pattern of destruction but there are certain common denominators.

Mr. FLOOD. And we are in the dark on the three.

Dr. MASLAND. We are in the dark on the three. But increasingly the spotlight is focused on them. Interest is accentuated by a very important discovery of a rare disease of the New Guinea natives called kuru.

For 5 or 6 years we have been culturing material from patients with that disease.

Mr. FLOOD. That is a brain condition?

Dr. MASLAND. It is a similar degenerative disease. There is an exciting development. We have found a virus in that disease and just within the last few months we have found a virus from another degenerative disease of humans called Jakob-Creutzfeldt. This is a widespread but uncommon disorder having many similarities to kuru.

There is another disease of interest—an encephalitis of childhood, which appears to be due to a latent form of measles virus.

Mr. FLOOD. You mean German measles?

Dr. MASLAND. No, regular measles. It looks now as though this was going to be pinned down within the very near future.

Now, it is these developments which have increased our interest in this area of investigation.

Within the NIH budget are funds for the construction of a new facility for this research. We consider it most crucial because these are dangerous viruses. We do not know how they act. Their latency may be 5 or 10 years. As the viruses are cultured in animals, their virulence becomes greater, and the hazard to our staff is increased. We need new, safer laboratories in this work.

Mr. FLOOD. What is the age bracket on these three, amyotrophic lateral sclerosis, multiple sclerosis, and Parkinsonism?

Dr. MASLAND. The first two are diseases of the young and middle aged. I have seen amyotrophic lateral sclerosis in individuals 13 or 14, usually it is around 40 to 50. With multiple sclerosis, the youngest patient I have seen started when she was only 6 or 7, but ordinarily it is a disease of 15 to 50. There appear to be at least two forms of Parkinsonism. There was an epidemic in 1920 of a peculiar form of encephalitis. As a residual, people developed Parkinsonism, and this almost certainly was due to a virus.

Fortunately, that epidemic has died out and most people feel at the moment that very few patients with Parkinsonism are having it as a result of that virus.

Mr. FLOOD. I see you have a special report on Parkinson's disease. We will place it in the record at this point.

(The report follows:)

SPECIAL REPORT: PARKINSON'S DISEASE

(Prepared January 1968 by the National Institute of Neurological Diseases and Blindness, Public Health Service, U.S. Department of Health, Education, and Welfare in connection with 1969 appropriations hearings)

Parkinson's diseases is one of the most crippling chronic disorders of the nervous system. Most frequently attacking people in their fifties and sixties, the disease is a matter of growing concern to the medical community because it is evidently increasing in prevalance along with the increase in average life span. Estimates of prevalance in the United States vary, ranging from 500,000 to as high as 1 million. As to incidence, reports indicate that between 25,000 and

43,000 new cases develop each year. Parkinsonism is known to afflict one out of every 1,000 people after the age of 50.

*Research and training support*

In a large-scale effort to help solve the problem of Parkinson's disease, the Institute is supporting many individual research projects in universities and other centers, and is conducting projects in its own laboratories in Bethesda, Md. Training in neurology, neurosurgery, neuropharmacology, and other relevant disciplines is being supported, and the Institute is working toward development of a coordinated national research program in the field.

*Centers*

Of considerable importance to this program are two large Institute-supported clinical research centers, at Columbia University and at the University of California at Los Angeles, where substantial basic and clinical work in Parkinson's disease and in the neurological sciences is in progress. Both of these centers have developed automated information services, so that scientists, teachers, and physicians anywhere in the world can obtain up-to-date research reports and other data rapidly. Bibliographies, indexes, and critical reviews are also produced.

*Conferences*

The Columbia center has conducted three large conferences, each focusing on an important aspect of Parkinson's disease research. The first of these, held in December 1964, was entitled "Thalamic Integration of Sensory and Motor Activities"; a second, a year later, was on "Biochemistry and Pharmacology of the Basal Ganglia," and a third, held in late 1966, was titled "Neurophysiological Basis of Normal and Abnormal Behavior." The meetings each attracted approximately 600 neurological scientists from this country and abroad, and drew together the most important research in these fields. Proceedings of each of the conferences have been published, each a landmark in Parkinson literature.

*Research approaches*

Research in Parkinson's disease is particularly active in the areas of biochemistry, neurophysiology, and pharmacology. The biochemical research is centered around the metabolism of substances in brain cells known as biogenic amines, studies of enzyme processes in brain stem nuclei, cells, and subcellular components, and investigations of neuromelanin, a pigment pathologically modified in Parkinson patients. Research in neurophysiology and anatomy continues to provide knowledge of structure and function on an increasingly finer scale, and pharmacologic work, closely tied in with biochemistry, continues in search of better drugs.

These fundamental studies of the chemistry, anatomy, and function of the brain have led to a new theory of disorders of movement control in parkinsonism. The theory envisages a balance within the nervous system between two parallel motor control pathways. The activity of one pathway is mediated through the biogenic amines; that of the other, through other chemical compounds—acetylcholine and cholinesterase. Parkinsonism occurs when there is an imbalance—when there is a reduction in activity of the biogenic amine pathway. Symptoms may be alleviated either by accomplishing a corresponding reduction in activity in the acetylcholine-mediated system, through drugs, or possibly surgery, or by increasing the activity of the parallel amine pathway. Interest has been aroused in the past year by reports of possible success in achieving this latter effect through treatment with large doses of the amine, L-DOPA. It is not yet known whether this compound will prove useful in therapy, but trials are in progress.

The genetics and epidemiology of parkinsonism are other areas of active research interest. Institute grantees reported in 1967 on a study of the natural history of the disease in 802 patients, and produced important new information. Among the highlights were the findings that parkinsonism confers no resistance to cancer (contrary to a widely held belief); that the relative mortality risk is less in men than in women; and that the death rate for all Parkinson patients is three times that of the general population of the same age, sex, and color. The scientists found no correlation between the rate of progression and age of onset, severe infection, positive family history, or other neurological disease. Nor did they find any evidence that modern treatments, though they relieve symptoms, have prolonged life.

An Institute study indicated a greater incidence of Parkinson's disease in the families of white patients than in the families of Negro patients. Although

the role of familial factors in parkinsonism is still unclear, these and similar studies add important data to existing knowledge.

Cause and cure of Parkinson's disease remain unknown. However, much can be done to control its symptoms, and highly encouraging research is in progress in a number of medical centers. The Institute is supporting a major fraction of this research, and there is good reason to expect the program to continue to gain in size, strength, and accomplishment. Gains made thus far, together with plans for the future, have justified an optimistic attitude among scientists, physicians, and others concerned that prevention and control of parkinsonism will ultimately be attained.

Mr. FLOOD. Is encephalitis contagious?

Dr. MASLAND. We do not know. In 1920, we did not have the techniques for culturing such agents. An agent was never discovered. We do not know how it was transmitted. It occurred shortly after the great influenza epidemic and was at the time thought to be a related virus. The general consensus of opinion now is that it was a separate virus which merely happened to come through the community at the same time.

CEREBRAL PALSY

Mr. FLOOD. Is cerebral palsy in the same area of being possibly related to virus infection?

Dr. MASLAND. Not in general; however, certain cases of cerebral palsy are a result of infection of the mother during pregnancy. This has been another one of the major areas of concern of our collaborative perinatal program, the study of virus infections during pregnancy and their effect on the unborn child. There are three infectious agents which we know have such harmful effects. One is German measles, and I believe that the testimony from the Allergy Institute will document the tremendous hope we have for the solution of that problem.

A second one is an agent called toxoplasmosis, which is an organism somewhat like the malarial parasite, a small parasite that gets into the brain.

And the third one is another virus called an inclusion virus.

Any of these three agents infecting the woman during pregnancy will injure the child.

EPILEPSY

Mr. FLOOD. What about epilepsy?

Dr. MASLAND. Toxoplasmosis is a cause of epilepsy. There are many causes of epilepsy.

Mr. FLOOD. Trauma?

Dr. MASLAND. Yes; trauma will cause epilepsy. Some forms of epilepsy probably depend heavily upon an inherited predisposition. Others may be the result of brain tumors. One of the earliest manifestations of the encephalitis I referred to a few moments ago is the occurrence of seizures. We do not know all of the causes of epilepsy, but we do know that anything that injures the brain may precipitate seizure.

MUSCULAR DYSTROPHY

Mr. FLOOD. Where does muscular dystrophy come in?

Dr. MASLAND. Muscular dystrophy is a paralysis and wasting of the muscle which is largely dependent upon an inherited disorder.

MONGOLISM

Mr. FLOOD. That brings up something of which we are hearing a great deal lately, the whole broad spectrum of mongolism.

Dr. MASLAND. I think most of the research on mongolism now is centered within the Child Health Institute. Our concern in mental retardation is primarily in the study of those brain diseases of childhood such as cerebral palsy and the others I have mentioned of which mental retardation is a symptom.

Mr. FLOOD. What is mongolism?

Dr. MASLAND. Mongolism or Down's Syndrome is a disorder which results from an abnormality of genes; the presence within the cell of an extra chromosome. This abnormality may be inherited through a similar abnormality of the mother. More commonly, however, it appears to reflect a disturbance in the final stages of the production of the ovum.

Mr. FLOOD. Why would it sometimes affect only one out of seven children?

Dr. MASLAND. You mean of one mother?

Mr. FLOOD. Yes.

Dr. MASLAND. The commonest form of mongolism is a form which occurs during the final stages of production of the ovum and would affect only the one ovum. So the other eggs would be normal.

An important area of research is to understand why that happens. It happens particularly in older women, more commonly after the age of 40.

Mr. FLOOD. If and when you isolate the cause, what would you do to attack it?

Dr. MASLAND. The cause is pretty well known. Attack is likely to be on some feature of the health of the mother prior to conception.

Mr. FLOOD Prior to conception?

Dr. MASLAND. Yes.

Mr. FLOOD. How would you know that?

Dr. MASLAND. We probably would not know that such-and-such a woman was predisposed. Hopefully, we might know that such-and-such circumstances were unfavorable and that women should be protected within that age group, if they are going to have children, by being given a hormone or a vitamin or whatever else might be required. This is pure speculation since we do not know what it is that deranges the egg-producing mechanism.

Mr. FLOOD. This problem is receiving your best care and attention?

Dr. MASLAND. That is correct.

Mr. FLOOD. Do you have any breakthroughs on this in sight?

Dr. MASLAND. Not that I could name.

Mr. LAIRD. Over in one of the other Institutes I think we have most of the funding in that area.

Dr. MASLAND. The major funding for mongolism is in the Child Health Institute.

REMARKS REGARDING THE DIRECTOR

Mr. FLOOD. Before I turn the questioning over to Mr. Laird, I want to observe that you have been with the Institute for some 10 years.

And now they say you are leaving, I am sorry to hear that; your loss will be a great one. Mr. Laird.

Mr. LAIRD. Dr. Masland, this is the last time you will be before us.

Dr. MASLAND. Yes, sir.

Mr. LAIRD. Where are you going to go?

Dr. MASLAND. To Columbia. I will be head of the department of neurology at Columbia.

Mr. LAIRD. When will you leave?

Dr. MASLAND. The 1st of June.

Mr. LAIRD. Certainly the National Institutes of Health is losing a number of good people. You are one the outstanding men who have brought the National Institutes to its position of eminence. Your departure is a great loss.

Dr. MASLAND. I would like to take this opportunity to emphasize that my leaving the Institute is not in any way a reflection of my lack of interest or my lack of satisfaction in the position I have had as Director of the Institute of Neurological Disease and Blindness. I wish also to express to you my appreciation for the depth of knowledge and interest which the members of this committee have always evidenced in their review of our programs.

It was a very difficult decision for me to leave what is and has been a tremendously exciting and challenging opportunity. I am leaving only to accept an unusually attractive new challenge.

Mr. LAIRD. That is all.

Mr. FLOOD. Mr. Casey?

Mr. CASEY. I have no questions, Mr. Chairman, but you have had the opportunity to associate with these distinguished gentlemen a long time. I am just beginning to get acquainted with them. All I knew about them was reading about them until I had the opportunity to come on this committee. I regret my tenure of association with some of them, like Dr. Masland, is going to be so short.

Mr. FLOOD. Mr. Shriver?

Mr. SHRIVER. No questions.

Mr. FLOOD. Doctor, I have before me charts which you presented to the committee for examination. They are in color and cannot be reproduced as such for the record.

Would you prepare for the record a set of tables which will translate these charts?

Dr. MASLAND. Very well.

Mr. FLOOD. Thank you.

(The information follows:)

RESEARCH SUPPORTED BY NINDB AND THE ECONOMIC LOSS OF NEUROLOGICAL AND SENSORY DISORDERS, FISCAL YEAR 1967

| Disease category | Research (dollars in thousands) | | | | | | | | | | | | | | | | | | Economic loss to the Nation (dollars in millions) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grants | | | Centers | | | Intramural | | | C. & F.R. | | | Contract | | | Total | | | | | |
| | Number | Dollars | Percent | Number | Dollars | Percent | Number | Dollars | Percent | Number | Dollars | Percent | Number | Dollars | Percent | Number | Dollars | Percent | | Dollars | Percent |
| 1. Neurological disorders of childhood | 111 | 6,503 | 71.6 | 0 | | | 33 | 1,247 | 14.3 | 108 | 964 | 10.6 | 5 | 321 | 3.5 | 257 | 9,035 | 12.5 | | 670 | 6.7 |
| 2 Aging | 52 | 875 | 38.7 | 3 | 835 | 37.0 | 5 | 209 | 9.0 | 1 | 2 | .1 | 2 | 341 | 15.0 | 63 | 2,262 | 3.1 | | 600 | 6.0 |
| 3. C.V.D. | 87 | 1,967 | 42.2 | 15 | 2,360 | 51.0 | 10 | 178 | 4.0 | 2 | 6 | 1.0 | 3 | 156 | 3.0 | 117 | 4,667 | 6.5 | | 1,500 | 15.0 |
| 4. Epilepsy | 73 | 1,795 | 56.0 | 3 | 551 | 17.0 | 16 | 666 | 22.0 | 1 | 81 | 2.5 | 2 | 92 | 3.0 | 95 | 3,185 | 4.4 | | 700 | 7.0 |
| 5. Sclerosing diseases | 78 | 2,835 | 89.3 | 0 | | | 2 | 114 | 3.6 | 4 | 182 | 5.7 | 1 | 43 | 1.4 | 85 | 3,174 | 4.4 | | 400 | 4.0 |
| 6. Neuromuscular | 104 | 3,053 | 81.0 | 2 | 263 | 7.0 | 14 | 449 | 12.0 | 0 | | | 0 | | | 120 | 3,765 | 5.2 | | 150 | 1.5 |
| 7 Infections of CNS | 18 | 526 | 48.0 | 0 | | | 2 | 142 | 13.0 | 3 | 432 | 39.0 | 0 | | | 23 | 1,100 | 1.5 | | 300 | 3.0 |
| 8. Trauma | 31 | 493 | 17.0 | 4 | 1,433 | 49.0 | 9 | 137 | 5.0 | 1 | 4 | 1.0 | 5 | 822 | 29.0 | 50 | 2,889 | 4.0 | | 3,400 | 34.0 |
| 9 Tumors of CNS | 44 | 818 | 42.0 | 0 | | | 19 | 1,130 | 58.0 | 0 | | | 0 | | | 63 | 1,948 | 2.7 | | 300 | 3.0 |
| 10. Neurological sciences | 428 | 10,445 | 78.6 | 5 | 935 | 7.1 | 36 | 1,803 | 13.5 | 1 | 3 | .02 | 3 | 99 | .78 | 473 | 13,285 | 18.3 | | | |
| 11 Noncategorical | 34 | 61 | 3.2 | 7 | 1,551 | 81.0 | 5 | 91 | 4.8 | 0 | | | 6 | 198 | 10.4 | 52 | 1,901 | 2.6 | | | |
| 12. Vision | 326 | 10,347 | 68.0 | 21 | 3,246 | 21.0 | 36 | 915 | 6.0 | 9 | 281 | 2.0 | 11 | 422 | 3.0 | 403 | 15,211 | 21.1 | | 1,500 | 15.0 |
| 13 Hearing | 154 | 4,917 | 80.6 | 7 | 843 | 13.8 | 4 | 194 | 3.1 | 2 | 44 | .7 | 1 | 105 | 1.7 | 168 | 6,103 | 8.4 | | 400 | 4.0 |
| 14. Speech and higher nerv. act | 34 | 1,068 | 65.0 | 2 | 398 | 24.0 | 4 | 61 | 3.6 | 1 | 5 | .3 | 1 | 105 | 6.4 | 42 | 1,637 | 2.3 | | 80 | .8 |
| 15 Other senses | 80 | 2,050 | 95.0 | 0 | | | 3 | 89 | 4.2 | 1 | 10 | .5 | 0 | | | 84 | 2,149 | 3.0 | | | |
| Total | 1,654 | 47,753 | | 69 | 12,415 | | 193 | 7,425 | | 134 | 2,014 | | 40 | 2,704 | | 2,095 | [1] 72,221 | 100.0 | | 10,000 | 100.0 |

[1] This research effort of $72,221,000 is 0.007 percent of the $10,000,000,000 economic loss to the Nation of neurological and sensory disorders.

JUSTIFICATION MATERIAL

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

National Institute of Neurological Diseases and Blindness

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation..... | $128,633,000 | $131,195,000 |
| Proposed transfer to "Indian health activities"..... | -1,677,000 | --- |
| Total..... | $126,956,000 | $131,195,000 |

Obligations by Activity

| Page Ref. | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|
| Grants: | | | | | | |
| Research..... | | $ 77,346,000 | | $ 80,038,000 | | +$2,692,000 |
| General research support grants..... | | (8,094,000) | | (7,430,000) | | (-664,000) |
| Scientific evaluation and planning. | | (155,000) | | (155,000) | | --- |
| Categorical clinical research centers... | | (3,150,000) | | (3,150,000) | | --- |
| Specialized research centers..... | | (800,000) | | (900,000) | | (+100,000) |
| Fellowships..... | | 3,805,000 | | 3,889,000 | | +84,000 |
| Training..... | | 18,780,000 | | 19,262,000 | | +482,000 |
| Direct Operations: | | | | | | |
| Laboratory and clinical research.. | 351 | 9,894,000 | 381 | 11,119,000 | +30 | +1,225,000 |
| Collaborative research and development..... | 194 | 10,190,000 | 194 | 10,206,000 | --- | +16,000 |
| Biometry, epidemiology and field studies... | 107 | 3,371,000 | 107 | 3,388,000 | --- | +17,000 |
| Training activities... | 3 | 73,000 | 3 | 74,000 | --- | +1,000 |
| Review and approval of grants..... | 106 | 2,418,000 | 113 | 2,499,000 | +7 | +81,000 |
| Program direction..... | 32 | 675,000 | 32 | 720,000 | --- | +45,000 |
| Total obligations... | 793 | 126,552,000 | 830 | 131,195,000 | +37 | +4,643,000 |
| Unobligated balance, reserve..... | 25 | 404,000 | | | -25 | -404,000 |
| Total obligations and reserve..... | 818 | 126,956,000 | 830 | 131,195,000 | +12 | +2,562,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions | 793 | 830 | +37 |
| Full-time equivalent of all other positions | 60 | 60 | --- |
| Average number of all employees | 801 | 850 | +49 |
| Personnel compensation: | | | |
| Permanent positions | $ 7,074,000 | $ 7,496,000 | +$422,000 |
| Positions other than permanent | 263,000 | 278,000 | +15,000 |
| Other personnel compensation | 88,000 | 92,000 | +4,000 |
| Total personnel compensation | 7,425,000 | 7,866,000 | +441,000 |
| Personnel benefits | 717,000 | 740,000 | +23,000 |
| Travel and transportation of persons | 453,000 | 560,000 | +107,000 |
| Transportation of things | 80,000 | 109,000 | +29,000 |
| Rent, communications, and utilities | 220,000 | 250,000 | +30,000 |
| Printing and reproduction | 50,000 | 80,000 | +30,000 |
| Other services | 737,000 | 775,000 | +38,000 |
| Project contracts | 9,050,000 | 9,235,000 | +185,000 |
| Payment to "National Institutes of Health management fund" | 6,106,000 | 6,413,000 | +307,000 |
| Supplies and materials | 1,085,000 | 1,090,000 | +5,000 |
| Equipment | 700,000 | 890,000 | +190,000 |
| Grants, subsidies, and contributions | 99,931,000 | 103,189,000 | +3,258,000 |
| Subtotal | 126,554,000 | 131,197,000 | +4,643,000 |
| Deduct quarters and subsistence charges | 2,000 | 2,000 | --- |
| Total obligations by object | 126,552,000 | 131,195,000 | +4,643,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $128,633,000 |
| Unobligated Balance, reserve | -404,000 |
| Proposed transfer to "Indian health activities" | -1,677,000 |
| 1968 total estimated obligations | 126,552,000 |
| 1969 estimated obligations | 131,195,000 |
| Total change | +4,643,000 |

| Increases | Base Positions | Base Amount | Change from Base Positions | Change from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of new positions authorized in 1968 | --- | --- | --- | 34,000 |
| 2. Annualization of the 1968 pay raise (in 1969) | --- | --- | --- | 111,000 |
| 3. One additional day of pay in 1969 | --- | --- | --- | 14,000 |
| Subtotal built-in | | | | 159,000 |
| B. Program | | | | |
| 1. Research grants | --- | 77,346,000 | --- | 2,692,000 |
| 2. Fellowships | --- | 3,805,000 | --- | 84,000 |
| 3. Training | --- | 18,780,000 | --- | 482,000 |
| 4. Laboratory and clinical research | 351 | 5,592,000 | 30 | 875,000 |
| 5. Review and approval | 106 | 1,332,000 | 7 | 25,000 |
| 6. Program direction | 32 | 411,000 | --- | 19,000 |
| Subtotal program increases | --- | --- | 37 | 4,177,000 |

Summary of Changes (con't)

C. Payment to "National Institutes of Health Management Fund" for centrally furnished services:

| | Base | | Change from Base | |
|---|---|---|---|---|
| | Positions | Amount | Positions | Amount |
| 1. Laboratory and Clinical Research..... | | 4,302,000 | | 255,000 |
| 2. Collaborative Research and Development..... | | 334,000 | | -11,000 |
| 3. Biometry, Epidemiology and Field Studies..... | | 116,000 | | 2,000 |
| 4. Review and Approval..... | | 1,086,000 | | 40,000 |
| 5. Program Direction..... | | 264,000 | | 21,000 |
| Subtotal Payment to Management Fund | | --- | | 307,000 |
| Total Program Increases.... | | --- | 37 | 4,643,000 |

Explanation of Changes

Research grants--The net increase of $2,692,000 includes $3,256,000 for support of the regular programs, a decrease of $664,000 for general research support grants and a $100,000 increase for specialized research centers.

Fellowships--The increase of $84,000 will provide for increased stipend costs and an increase of 9 postdoctoral awards and one career development award.

Training grants--The increase of $482,000 will sustain the graduate training grants program in the various fields of neurological and sensory disorders.

Laboratory and clinical research--The program increase of $875,000 will provide funds in the new facility for the support of 30 new positions required for the expanded programs of intramural research and for new equipment and supplies.

Review and approval of grants--The increase of $25,000 and 7 positions will provide continued support required for the review and analysis of the grant programs of this Institute.

Program direction--The increase of $19,000 will provide additional support for the administrative staff in the Office of the Director.

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301--Research and Investigations in general..... | Indefinite |
| Title IV, Part D--National Institute of Neurological Diseases and Blindness... | Indefinite |

PUBLIC HEALTH SERVICE ACT

Authorizing Legislation

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume V.

Title IV, National Research Institutes, Part D, National Institute on Arthritis, Rheumatism, and Metabolic Diseases, National Institute on Neurological Diseases and Blindness, and other Institutes.

"Sec. 431 (a) The Surgeon General shall establish in the Public Health Service....an institute for research on neurological diseases (including epilepsy, cerebral palsy, and multiple sclerosis) and blindness...."

"Sec. 433 (a) Where an institute has been established under this part, the Surgeon General shall carry out the purposes of section 301 with respect to the conduct and support of research relating to the disease or diseases to which the activities of the institute are directed, through such institute and in cooperation with the national advisory council established or expanded by reason of the establishment of such institute. In addition, the Surgeon General is authorized to provide training and instruction in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and, in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions.

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Explanation of Transfers

| Proposed transfer to: | 1968 Estimate | 1969 Estimate | Purpose |
|---|---|---|---|
| "Indian health activities" | $1,677,000 | --- | To provide for increased pay costs in 1968. |

## Justification

### National Institute of Neurological Diseases and Blindness

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 793 | 8,142,000 | 830 | 8,606,000 | +37 | + 464,000 |
| Other expenses..... | ___ | 118,410,000 | ___ | 122,589,000 | ___ | +4,179,000 |
| Total..... | 793 | 126,552,000 | 830 | 131,195,000 | +37 | +4,643,000 |

### General Statement

This Institute is concerned with a variety of diseases which afflict the brain and the sense organs. Long-term disability is the result of disorders such as cerebral palsy, epilepsy, multiple sclerosis, muscular dystrophy, parkinsonism, deafness, and blindness, while cerebrovascular disease (stroke) is the third largest cause of death in this country as well as invaliding many others. Progress against these inadequately understood diseases would relieve mankind of some of its heaviest disease burdens.

These neurological and sensory disorders fall into 14 major program areas, each subject of a specifically focused research effort. The research effort in each of these areas is carried out through extramural project research grants, center or program project research grants, intramural research projects, collaborative and field research projects and contract research projects.

The program areas and the distribution of the research effort for each category in 1967 was as follows:

The chronic neurological disorders of childhood include all those diseases of the nervous system which occur in early life whether they are acute or chronic. This is being pursued through some 263 projects, 117 of which are research grants, 33 are intramural projects, 108 are collaborative and field projects, and 5 are contracts.

The chronic neurological disorders of aging are those diseases of the nervous system which manifest themselves late in life, but are chronic and debilitating. In this area we have 66 projects, 55 of which are extramural grants, 2 centers, 5 intramural projects, 1 collaborative and field project, and 2 contracts.

The cerebrovascular diseases include all those disorders of the central nervous system related to blood circulation including stroke. Here, there are 119 projects, 89 in grants, 16 in centers, 10 intramural, 2 collaborative and field, and 3 contracts.

Epilepsy and convulsive disorders are those conditions in which recurrent seizures require constant medication or treatment. There are some 97 projects in this area, 25 of which are grants, 2 intramural projects, 4 collaborative and field projects, and 3 centers.

Sclerosing disorders include such diseases as multiple sclerosis, amyotrophic lateral sclerosis, and others which are chronic and incapacitating but for which there is no certain cause or treatment. There are 88 projects of which 81 are grants, 2 intramural, 4 collaborative and field, and 1 contract.

Neuromuscular and muscular disorders of the nervous system are those diseases which involve both nerves and muscles in their interactions. These may occur at different periods of life, but are chronic and, again, incapacitating. There are some 124 projects here, 108 as research grants, 2 centers, and 14 intramural projects.

Infections of the nervous system are all those diseases caused by known infectious agents whether bacterial, virus, rickettsial, fungus, or other. There are some 23 projects in this area, 18 extramural grants, 2 intramural projects, and 3 collaborative and field projects.

Accident and injury of the nervous system includes all those physical agents which can accidentally cause injury to the nervous system. In this area there are some 53 projects of which 39 are extramural grants, 5 centers, 4 intramural, 1 collaborative and field, and 5 contract projects.

Tumors of the nervous system include all the neoplastic growths which occur within the confines of the nervous system and include the metastatic tumors of the nervous system which originate elsewhere in the body. There are 55 projects, 36 grants, 19 intramural projects.

Other neurological disorders and neurological sciences include all kinds of research which may relate to several of these disease categories or all of them. This is basic research on the nervous system which has wide application in many problems. There are 483 projects, 423 of which are extramural grants, 5 are centers, 36 are intramural projects, 1 collaborative and field, and there are 3 contract projects.

Vision and diseases of the eye include all those things relative to vision. There are 420 projects, 324 of which are extramural grants, 21 centers, 36 intramural projects, 9 collaborative and field, and 11 contracts.

Hearing, equilibrium, and problems of the ear are being investigated in 174 projects, as 160 grants, 9 centers, 4 intramural projects, 2 collaborative and field projects, and 1 contract.

Speech and higher nervous activity include 42 research projects of which 35 are grants, 1 center, 4 intramural, 1 collaborative and field project, and 1 contract.

Other sensory disorders (taste, smell, touch, etc.) encompass 86 research projects, 82 of which are grants, 3 intramural, 1 collaborative and field project, and no contracts.

The Institute maintains an overview of each of these areas through special task forces, Advisory Council Subcommittees, and its scientific information network now centered in four of the Nation's strongest university libraries and research laboratories. These facilities have been developed to advise the Institute staff of research needs and current progress.

From the outset, the use of focused and directed research efforts has been a major part of the Institute's program. For example, the cooperative study of retrolental fibroplasia, completed in 1955 at a cost of approximately $50,000, provided the answer to the cause of this form of blindness in infants and ultimately saved the country over $100 million for each year that this discovery was advanced by the study. The longest Institute study of this type is the Collaborative Perinatal Project, which is now in its eighth year. Other cooperative and collaborative studies are now in progress, and a major segment of direct research is devoted to the direction and coordination of these investigations, frequently using the contract mechanism.

Faced from the outset with a critical shortage of the highly specialized scientists required for neurological and sensory research, the Institute has devoted approximately 25 percent of its grant funds to the training of personnel. Former trainees form an important segment of developing programs, such as the newly established stroke centers. The expanding number and size of medical schools and specialty training programs are increasing the manpower demands from our training programs. These must grow to meet these needs.

The research supported by the Institute in these major program areas is discussed further in the following sections.

Research Grants

| | 1968 Estimate Amount | 1969 Estimate Amount | Increase or Decrease Amount |
|---|---|---|---|
| Research Projects..... | 65,147,000 | 68,403,000 | +3,256,000 |
| Special Programs..... | 12,199,000 | 11,635,000 | -564,000 |
| Total Research Grants..... | 77,346,000 | 80,038,000 | +2,692,000 |

## Introduction

For the development and implementation of its attack on disorders of the brain and sense organs, the National Institute of Neurological Diseases and Blindness utilizes several methods of research support. The method most generally used is that of the regular research grant to support the independent investigator. In some instances, a number of extramural scientists work together as a group on cooperative projects requiring massive data and broad geographical and scientific discipline representation. Institute scientists themselves may actually participate in a collaborative project with non-governmental groups. The more difficult problems, such as research on stroke or on head injuries, require that there be assembled within a single institution a multi-disciplinary attack on a problem area. For this, a program project or clinical research center is established. Planning grants are frequently necessary to aid in the initial development of such complex centers. For some types of research, for example blindness, clinical investigations can be carried out without the necessity of hospitalization. For this, outpatient clinical research units are being provided.

## Program Plans for 1968 and 1969

In 1968, approximately 1,605 regular research projects totalling $65,147,000 will be awarded by the Institute. With the funds requested for 1969, the Institute will award approximately 1,612 regular research projects totalling $68,403,000.

The budgets for 1968 and 1969 continue to reflect an anticipated requirement for additional funds as a result of the recently authorized cost sharing arrangements for new and renewal research grants. This plan considers the full direct and indirect costs of the project in arriving at the federal and non-federal share.

Of the increase, $3,256,000 will be used to meet the rising costs of ongoing or non-competing research projects. This research will continue the emphasis in fields of epilepsy, parkinsonism, disorders of vision, brain injury, disorders of speech and hearing, and stroke. New programs will be initiated as described below.

## Regular Research Projects

Although a program of approximately 1,612 regular research projects is difficult to summarize in a few sentences and the immediate results may be less readily defined than is the case with some other types of support, their importance to the mission of NINDB cannot be overemphasized. They constitute the major portion of the extramural research program. Support for individual projects varies from a few thousand to hundreds of thousands of dollars per year. They represent the ideas and approaches of the individual, independent scientist. Some are largely clinical. Others represent an excellent combination of clinical and basic research. The majority of them are fundamental studies, however, not only on the causes, treatment, and prevention of all of the health problems mentioned below, but on the very mechanisms by which cells, genes, viruses, protein molecules, and other basic biological entities reproduce and function. From experience in the past, it has been research such as this that has opened up new frontiers in science and which has provided much of the information that is subsequently helpful to the patient. Building upon this broad base of independent research, the Institute is establishing special projects and programs directed toward specific categorical objectives. A well rounded program for each of the institutes' disease problems is thus being created.

## Disorders of Vision

In November 1964 an ad hoc Subcommittee on Vision and Its Disorders was established on the recommendation of NANDB Council. The Subcommittee and its task forces spent two years in an effort to "review the present status of knowledge about the major causes of blindness and visual disability and to summarize the most pressing problems for investigation as well as the most promising research leads." The report of that expert panel includes 24 specific recommendations and provides a basis for the development of additional national activities in this important area to be carried out with the advice of a permanent Subcommittee on Vision and Its Disorders. Volume II of the Report, containing scientific status papers, provides a comprehensive scientific review of the fields of vision and blindness, and is now being made available to the scientific community.

In addition to the program of support for regular research projects in the field of blindness, support is now being provided for 9 clinical research centers for blindness and visual disorders, each concentrating primarily on special clinical problems such as cataract, glaucoma, disorders of the cornea, infections of the eye, and disturbances of eye movement, but retaining a broad approach to the overall problem of blindness. An additional

3 centers are providing information about the fundamental mechanisms by which light impulses are converted to nervous energy and transmitted to the brain for interpretation. Thus, they are broadly concerned with sensory and perceptual disorders.

The program of vision outpatient clinical research centers initiated on a pilot basis in 1967 and 1968 is proving highly successful and will be expanded. Heretofore, the participation of the large outpatient population with visual disorders in research has been limited by inadequate facilities. The outpatient center program is now rectifying this problem. Approximately 12 outpatient centers will be in operation in 1968.

In accordance with recommendations of the ad hoc Committee, a series of working and planning conferences are being supported. The problems of refractive errors of vision (near-sightedness) have been reviewed. A workshop on the effects on the eye of drugs and toxins has been organized, and a center for such studies is being established.

## Head Injury

The Institute has been progressively increasing its program of fundamental research on the basic mechanisms of brain injury. However, for initiation and strengthening of clinical studies, head injury centers are needed. Following an important planning conference, a program of planning grants for Head Injury Clinical Research Centers was initiated in 1967. This program, which now includes 6 such grants, will be expanded in 1969 and will result in the development and implementation of proposals for the establishment of a full-scale Head Injury Clinical Research Centers program. These Centers will concentrate on epidemiology; the physical forces involved in causing head injury; improved diagnostic and therapeutic procedures; the physiological consequences of head injury; the structure and function of the blood-brain barrier; and the problems of brain swelling after injury.

## Stroke

Stroke is one of the leading causes of death and commonly strikes at a time when the individual is at his most productive stage. For those who survive, the disease usually entails lifelong physical disability and mental incapacity. Aphasia, paralysis and incontinence are too often the tragic consequences of stroke.

Among the needs for more effective treatment of stroke are the development of tests and methods to anticipate and prevent complete obstruction of brain blood vessels. Ways to reopen obstructed cerebral vessels and to replace or supplement vessels which are diseased beyond repair must be devised and improved.

Sixteen clinical research centers for stroke research are presently being supported. It is proposed to support an additional seven such centers.

By means of planning grants, development of stroke clinical research centers will be encouraged in additional geographic areas and in institutions which have clinical material that otherwise would not be utilized for lack of the necessary extensive financial resources. In addition, support for outpatient clinical research centers in this area was initiated in 1967, and will be extended in 1968 and 1969. This provides important access to ambulatory patients who frequently are the best source of information regarding early diagnosis of stroke and mechanisms concerned with restoration of an adequate functional state.

The main thrust of the Institute's attack on the stroke problem is by means of these clinical research centers. Support of much basic laboratory research is still clearly necessary to complement the clinical research center program which is providing the means to translate laboratory findings about the causes, the treatment, and the prevention of stroke into clinically effective measures. Additional contributions are being brought to bear on these problems through support of cooperative studies in the surgical and medical treatment of aneurysms and in the value of drugs to reduce hypertension for the prevention of stroke.

Disorders of Human Communication (Hearing, Language and Speech)

An ad hoc Task Force on Disorders of Human Communications which has been organized by the Institute is reviewing the present state of research and the problems of communicative disorders. Early detection and proper management before these disorders become firmly established is essential. The urgency of early detection emphasized the importance of the participation of medical research and public health personnel.

For this reason, clinical research centers are being established to provide for research on diagnosis and treatment and for the training of professional personnel. These centers are multidisciplinary and include investigators in many aspects of human communication. The Institute looks primarily to these centers for the major developments in the detection, diagnosis, therapy, and natural history of communicative disorders. To a greater degree than in almost any other field, the individual with a communicative disorder is likely to be an outpatient so that this is one of the areas to which the concept of outpatient clinical research units is being applied. In order that full advantage be taken of the geographic diversity of clinical material, this acitvity is being gradually expanded in all regions of the country.

Muscular Dystrophy

Muscular dystrophy is one of a group of diseases characterized by gradual wasting of muscles which is prone to occur in children of early school age. Available treatments are poor or nonexistent, and the occurrence of spontaneous temporary remissions make accurate evaluation of therapy very difficult. A number of individual projects have advanced our knowledge of the basic biochemical and structural defects in muscular dystrophy patients. Within two institute-supported clinical centers, multidisciplinary attacks on this problem have been developed.

## Epilepsy and Parkinsonism

In the important areas of the paroxysmal disorders, notably epilepsy, and of the chronic neurological disorders of aging, notably Parkinsonism, the Institute is engaged in attacks along a broad front. The relatively modest support via regular research grants is being bolstered by current support of three epilepsy centers and two centers for Parkinsonism and allied disorders. In addition support of a number of program projects in relevant basic disciplines, such as neuropharmacology and neurochemistry, has been undertaken and will be expanded. In the cases of both epilepsy and Parkinsonism, recent emphasis on development of new drugs will shortly require availability of extensive clinical facilities for testing and evaluation. The expansion of center programs, including the possibility of those of the outpatient type for epilepsy and Parkinsonism, is planned for 1969.

## Neuroviruses and Sclerosing Disorders

It has been well known for many years that some types of viruses, such as the poliomyelitis virus, have a special affinity for the nervous system. Recently a growing interest and concern has developed within the scientific community with regard to the presence and effects of so-called "slow" or "latent" viruses which apparently lie dormant for many years.

For the past several years, the Institute has been developing a program to search for viruses as a cause of such chronic neurological diseases as multiple sclerosis, amyotrophic lateral sclerosis, Parkinsonism and the encephalitides of childhood.

In view of the very great potential importance of this field, support for research in this field should be expanded as rapidly as competent investigators can be found who are willing to undertake such a difficult and long range problem. In 1969, two additional laboratories can be established in this potentially fruitful area of investigation.

Whether or not other sclerosing disorders, notably multiple sclerosis and amyotrophic lateral sclerosis, prove to be caused by "slow" viruses, there is very great need for a more concerted attack on these currently hopeless clinical problems. In 1969 one or two program projects or centers for research on multiple sclerosis can be established.

## Research Grants Program Analysis

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Chronic Neurological Disorders of Childhood | $ 3,400,000 | $ 3,530,000 | +$ 130,000 |
| Chronic Neurological Disorders of Aging | 1,879,000 | 1,973,000 | + 94,000 |
| Cerebrovascular Disorders | 4,887,000 | 5,281,000 | + 394,000 |
| Epilepsy and Related Paroxysmal Disorders | 2,592,000 | 2,772,000 | + 180,000 |
| Sclerosing Disorders | 2,983,000 | 3,133,000 | + 150,000 |
| Muscular & Neuromuscular Disorders | 3,730,000 | 3,865,000 | + 135,000 |
| Infectious Diseases | 529,000 | 555,000 | + 26,000 |
| Accident and Injury | 1,555,000 | 1,783,000 | + 228,000 |
| Tumors of Nervous System | 757,000 | 846,000 | + 89,000 |
| General | 13,890,000 | 14,408,000 | + 518,000 |
| Disorders of Vision | 15,954,000 | 16,619,000 | + 665,000 |
| Disorders of Hearing and Equilibrium | 6,984,000 | 7,332,000 | + 348,000 |
| Disorders of Speech & Other Higher CNS Functions | 1,863,000 | 2,007,000 | + 144,000 |
| Disorders of Other Senses | 2,365,000 | 2,432,000 | + 67,000 |
| Non-Categorical | 1,779,000 | 1,867,000 | + 88,000 |
| Total Regular Research Grants | $65,147,000 | $68,403,000 | +$3,256,000 |

## Distribution of Research Grants

| | 1968 No. | 1968 Estimate Amount | 1969 No. | 1969 Estimate Amount | Increase of Decrease No. | Increase of Decrease Amount |
|---|---|---|---|---|---|---|
| 1. Non-competing | 1,080 | $42,813,000 | 1,175 | $46,069,000 | +95 | +$3,256,000 |
| 2. Competing | 525 | 20,784,000 | 437 | 19,834,000 | -88 | - 950,000 |
| 3. Supplementals | (180) | 1,550,000 | (240) | 2,500,000 | (+60) | + 950,000 |
| 4. Subtotal Regular Program | 1,605 | 65,147,000 | 1,612 | 68,403,000 | + 7 | + 3,256,000 |
| 5. General Research Support Grants | | 8,094,000 | | 7,430,000 | | - 664,000 |
| 6. Scientific Evaluation | | 155,000 | | 155,000 | | --- |
| 7. Categorical Clinical Research Centers | | 3,150,000 | | 3,150,000 | | --- |
| 8. Specialized Research Centers | | 800,000 | | 900,000 | | + 100,000 |
| 9. Total Research Grants | 1,605 | 77,346,000 | 1,612 | 80,038,000 | + 7 | + 2,692,000 |

Fellowships

| | 1968 Estimate Amount | 1969 Estimate Amount | Increase or Decrease Amount |
|---|---|---|---|
| Total fellowships..... | $3,805,000 | $3,889,000 | + $84,000 |

## Introduction

The research fellowship programs of the National Institute of Neurological Diseases and Blindness are designed primarily to encourage specialized advanced research training. They provide the financial support necessary for clinicians and laboratory scientists to become qualified for research on problems of disease and disorder of the nervous system, vision, hearing, and human communication. A group of scientists highly skilled in diversified fields such as neuroanatomy, neurophysiology, neuropathology, neurochemistry, audiology, speech pathology, biophysics, ophthalmology, otolaryngology, and pharmacology is essential for the needed advances in solving these problems. This research group must become skilled in the use of the most up-to-date techniques and instrumentation and in their application to medical research. The fellowship programs have proven effective in meeting these objectives. A significant proportion of the research scientists whose projects are now being supported by NIH are men who received training under this program.

## Program Plans for 1968 and 1969

### Postdoctoral Fellowships

Postdoctoral fellowships provide financial support for the continuing study of scientists who have just completed doctoral training. Because of a PHS-wide increase last year in the amounts of postdoctoral fellowships stipends and in research allowances, the estimated proportion of fellowships that can be funded in 1969 will be fewer than in 1968. Emphasis will continue on training in scientific fields relevant to basic and clinical research on problems of epilepsy, head injury, cerebrovascular disease, vision, human communication, and other neurological and sensory disorders.

### Career Development Awards Program

Career Development Awards assure salary support over a 5-8 year period for selected scientists who have completed their formal research training but who require additional specialized experience. It provides them with an opportunity to develop a chosen line of research and to become established as independent investigators. These awards are particularly important for the well-trained research-clinician, who is thus enabled

to devote himself completely to the development of the academic career for which he has had long years of clinical and research training. Many individuals are needed, who combine firsthand knowledge of neurological and sensory disease with extensive knowledge in one or more of the basic science areas. Of the total increase requested for the Fellowships program, 12 percent or $10,000 will be applied to the career development program.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting... | 98 | $2,263,000 | 101 | $2,324,000 | +3 | +$61,000 |
| b. Competing..... | 72 | 860,000 | 79 | 940,000 | +7 | + 80,000 |
| 2. Supplementals..... | (97) | 91,000 | (69) | 75,000 | -(28) | - 16,000 |
| 3. New Grants | 49 | 591,000 | 49 | 550,000 | --- | - 41,000 |
| 4. Total fellowships | 219 | 3,805,000 | 229 | 3,889,000 | +10 | + 84,000 |

Fellowships (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Postdoctoral..... | 91 | $ 900,000 | 100 | $ 960,000 | +9 | +$60,000 |
| 2. Research Career: | | | | | | |
| a. Career..... | 14 | 390,000 | 14 | 404,000 | --- | + 14,000 |
| b. Development.... | 114 | 2,515,000 | 115 | 2,525,000 | +1 | + 10,000 |
| 3. Total fellowships.. | 219 | 3,805,000 | 229 | 3,889,000 | +10 | + 84,000 |

Training Grants

| | 1968 Estimate Amount | 1969 Estimate Amount | Increase or Decrease Amount |
|---|---|---|---|
| Total training grants.... | $18,780,000 | $19,262,000 | + $482,000 |

## Introduction

The Training Grants program of the National Institute of Neurological Diseases and Blindness provides support to institutions for establishing, improving, or expanding training programs designed to prepare clinical and laboratory scientists for research & academic careers, and for careers in organized community service and public health in the disciplines relevant to the nervous system, the neuromuscular system, vision, hearing, and human communication. The responsibility for future advances in understanding, preventing, and treating successfully the neurological and sensory disorders rests essentially with this group of clinical and laboratory scientists who are trained as leaders in teaching and research.

In 1968 the Institute expects to support approximately 301 training programs, and through these programs provide training for about 1,640 trainees and special fellows.

The impact of the training programs to date has resulted in nearly tripling the number of scientists and scientist-clinicians devoted to teaching and research in these critical areas. In terms of meeting even a minimum level of national needs, however the program is just beginning to achieve its objectives. During 1968, surveys are being planned or have been undertaken to assess in depth the effectiveness of certain training programs, such as those in ophthalmology, or the needs for certain other programs, such as clinical neurochemistry and molecular biology. On the basis of population forecasts, the opening of a score or more new medical schools in the next decade, and the increasing demands of community and regional medical programs, the need for highly trained clinicians, teachers and researchers in the areas of neurological and sensory disorders will continue to be most pressing and acute. Present projections suggest that we may in fact not be able to keep pace with the growing needs. In 1968 the available funds permitted the maintenance of a number of ongoing training programs. Others were terminated in order to provide funds for the establishment of a few new projects in the most critical areas. In 1969, because of some increase in costs, the additional funds will be used simply to maintain the present level of activity.

PROGRAM ANALYSIS

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| 1. Neurology | $ 5,026,000 | $ 5,179,000 | + $ 153,000 |
| 2. Ophthalmology | 3,057,000 | 3,149,000 | + 92,000 |
| 3. Otolaryngology | 2,457,000 | 2,531,000 | + 74,000 |
| 4. Communicative Disorders | 183,000 | 188,000 | + 5,000 |
| 5. Medical Audiology | 382,000 | 393,000 | + 11,000 |
| 6. Neuroanatomy | 263,000 | 271,000 | + 8,000 |
| 7. Neurochemistry | 163,000 | 168,000 | + 5,000 |
| 8. Neuropathology | 654,000 | 673,000 | + 19,000 |
| 9. Neuropharmacology | 232,000 | 239,000 | + 7,000 |
| 10. Neurophysiology | 705,000 | 726,000 | + 21,000 |
| 11. Neuroradiology | 250,000 | 257,000 | + 7,000 |
| 12. Neurosurgery | 598,000 | 616,000 | + 18,000 |
| 13. Experimental Neurosurgery | 111,000 | 114,000 | + 3,000 |
| 14. Neurological Basic Science | 101,000 | 104,000 | + 3,000 |
| 15. Ophthalmic Basic Science | 53,000 | 54,000 | + 1,000 |
| 16. Ophthalmic Pathology | 124,000 | 127,000 | + 3,000 |
| 17. Otolaryngology & Audiology | 264,000 | 271,000 | + 7,000 |
| 18. Otological Pathology | 117,000 | 120,000 | + 3,000 |
| 19. Pediatric Neurology | 557,000 | 573,000 | + 16,000 |
| 20. Medical Neurology & Public Health | 28,000 | 29,000 | + 1,000 |
| 21. Sensory Physiology | 121,000 | 124,000 | + 3,000 |
| 22. Speech Pathology | 184,000 | 189,000 | + 5,000 |
| 23, Speech Pathology & Audiology | 145,000 | 149,000 | + 4,000 |
| 24. Vision Psychophysiology | 10,000 | 11,000 | + 1,000 |
| 25. Cerebrovascular | 420,000 | 432,000 | + 12,000 |
| 26. Scientific Evaluation & Planning | 175,000 | 175,000 | + --- |
| Total Graduate Training Grant Program | $16,380,000 | $16,862,000 | + $482,000 |

Traineeships

Program Analysis

| | Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|---|
| 1. | Neurology | 16 | 16 | --- |
| 2. | Opthalmology | 23 | 23 | --- |
| 3. | Otolaryngology | 4 | 4 | --- |
| 4. | Audiology-Speech Pathology | 5 | 5 | --- |
| 5. | Biochemistry | 3 | 3 | --- |
| 6. | Biophysics | 3 | 3 | --- |
| 7. | Neuroanatomy | 4 | 4 | --- |
| 8. | Neurochemistry | 8 | 8 | --- |
| 9. | Neurocytology | 2 | 2 | --- |
| 10. | Neuroendocrinology | 3 | 3 | --- |
| 11. | Neuropathology | 24 | 24 | --- |
| 12. | Neuropharmacology | 3 | 3 | --- |
| 13. | Neurophysiology | 14 | 14 | --- |
| 14. | Neuroradiobiology | 15 | 15 | --- |
| 15. | Neurosurgery | 7 | 7 | --- |
| 16. | Ophthalmic Pathology | 10 | 10 | --- |
| 17. | Pediatric Neurology | 45 | 45 | --- |
| 18. | Physiological Psychology | 2 | 2 | --- |
| 19. | Sens. Physiology-Pathology | | | |
| | (Vision) | 3 | 3 | --- |
| | (Otolaryngology) | 3 | 3 | --- |
| 20. | Speech and Hearing Mech. | 2 | 2 | --- |
| 21. | Virology-Immunology | 5 | 5 | --- |
| 22. | Cerebrovascular | 14 | 14 | --- |
| | Total | 218 | 218 | --- |

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting . . . | 223 | $12,400,000 | 225 | $12,900,000 | + 2 | +$ 500,000 |
| b. Competing . . . . | 139 | 4,000,000 | 152 | 4,487,000 | +13 | + 487,000 |
| 2. Supplementals . . . . | (70) | 235,000 | (70) | 230,000 | --- | - 5,000 |
| 3. New Grants . . . . . | 157 | 1,970,000 | 139 | 1,470,000 | -18 | - 500,000 |
| 4. Scientific evaluation and planning . . . . | (5) | 175,000 | (5) | 175,000 | --- | --- |
| 5. Total training grants. | 519 | 18,780,000 | 516 | 19,262,000 | - 3 | + 482,000 |

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate . . . . . | 301 | $16,205,000 | 298 | $16,687,000 | - 3 | + 482,000 |
| 2. Traineeships . . . . . | 218 | 2,400,000 | 218 | 2,400,000 | --- | --- |
| 3. Scientific evaluation and planning . . . . | (5) | 175,000 | (5) | 175,000 | --- | --- |
| 4. Total training grants. | 519 | 18,780,000 | 516 | 19,262,000 | - 3 | + 482,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 351 | 3,885,000 | 381 | 4,260,000 | +30 | +375,000 |
| Other expenses..... | | 6,009,000 | | 6,859,000 | | +850,000 |
| Total..... | 351 | 9,894,000 | 381 | 11,119,000 | +25 | +1,225,000 |

Program Plans for FY 1968 and 1969

Clinical Research

Medical Neurology

Clinical investigations in this Intramural Branch are concentrated on neuromuscular diseases and degenerative diseases of the nervous system. They involve application directly to the patient of the newest aspects of basic research techniques in histochemistry, biochemistry, immunology, electron microscopy, tissue culture, autoradiography and electromyography. Two new neuromuscular diseases, focal loss of muscle fiber cross-straitions and hypotrophy of Type I muscle fibers with internal nuclei, and a new form of recurrent neuropathy, a-lipoprotein deficiency or Tangier disease, have been described.

Neuroradiologic studies have produced new techniques in angiography of the brain and spinal cord, and in brain scanning with radioisotopes injected both intravenously as well as into the cerebrospinal fluid to follow its movements.

Neuropharmacologic studies have further clarified the chemistry of relaxation and contraction of slow striated muscle, the mechanical characteristics of active twitch muscle, the effects of several snake venoms on the blood brain barrier and the neuromuscular junction. The last is in collaboration with Ein Shams University, Cairo, Egypt (PL-480 program).

This Branch has continued to train investigators and technicians in the methods of clinical research in neuromuscular disease and served as referral center for the histochemical analyses of muscle biopsies.

Surgical Neurology

The Surgical Neurology Branch is applying surgical and laboratory techniques to problems of head injury, epilepsy, cerebral palsy, and mental retardation. Surgical techniques are also being developed and refined.

Head injury and its accompanying brain damage are important causes of death and disability. Through means of high-speed photography, X-ray, and various

physiological recording devices, the immediate effects of brain injury are being observed and analyzed. In addition, histochemical and electron microscopy studies of the injured brain are being made. A system of classifying and coding patients with head injury has been developed and is being used, while a few highly selected patients with severe injury to the brain stem are being studied directly.

Cerebral edema is an important complication of head injury and brain disease. The occurrence of brain swelling within the closed cerebral cavity greatly aggravates the results of injury. Investigations of the disturbed permeability of the blood brain barrier through the use of radioactive tracers and other specialized techniques are directed toward determining a method to modify this reaction.

The effect of cold and drugs on epilepsy and drugs on brain tumors are being studied. Using a new technique, the brain is cooled while anticonvulsant drugs are given by vein. Similarly, for the treatment of brain tumor, anti-carcinogenic drugs are instilled directly into the brain cavities of the afflicted patient.

Children with inborn and acquired brain lesions as well as those suffering from mental retardation are being studied by clinical, laboratory, chromosomal, and biochemical techniques in an attempt to ascertain the nature and cause of these defects and afford better management and prevention.

Ophthalmology

This Branch is studying the mechanisms through which the visual image is converted to coded messages within the eye and then interpreted within the central nervous system. These investigations have produced a new theory of the basic mechanisms whereby light falling upon the retina generates nerve activity. Investigations of the electrical responses of the eye (electro-retinogram and electro-oculogram) have been used for the diagnosis of diseases leading to blindness, such as retinitis pigmentosa, for the early recognition of degeneration of the retina produced by drugs, specifically chloroquine, and for the differentiation of various forms of night blindness.

Glaucoma investigations are concentrating on the mechanisms producing the increased intraocular pressure characteristic of that disorder, and on the development, animal testing, and clinical evaluation of new drugs.

The treatment of inflammations of the eye also is being studied with particular attention to compounds suppressing toxoplasma infection and the use of antimetabolites in diseases in which an immunologic mechanism is suspected. The lens epithelium has proven an excellent experimental system to analyze the effect of anticancer drugs on a cellular level.

Electroencephalography and Clinical Neurophysiology

This Branch maintains a diagnostic service in electroencephalography widely called upon by the entire Clinical Center.

Investigations are centering on an understanding of the essential brain mechanisms underlying epilepsy and related brain abnormalities in both human and experimental situations. The electrical activity of the brain cells is being recorded under normal and abnormal conditions by means of fine needle electrodes (micro-electrodes). Such knowledge is essential to an understanding of the deviations of electrical activity underlying the epileptic seizure.

Other interests relate to mechanisms of abnormal movements such as those occurring in Parkinson's disease and related disorders.

Laboratory of Neuropathology and Neuroanatomical Sciences

The understanding of neurological disorders requires a precise knowledge of the normal structures of the nervous system and of the demonstrable changes which occur in these structures as a result of disease.

Normal structures are being studied at several levels. The electron microscope is used to investigate intimate details of the individual cells and of their intercellular connections, the synapses. The response of these individual units to physiological and pathological conditions is also being observed.

Through a study of the organizational patterns of these neural elements, their nature and function in the overall complex organization of the brain is being elucidated. This laboratory is especially emphasizing the study of the brain structures involved in hearing.

An important destructive process which is under intensive investigation is brain swelling (edema) which occurs subsequent to a variety of noxious conditions such as asphyxia, head injury, or over-exposure to ionizing radiation.

Neurophysiology

The work of this laboratory is directed toward our understanding of fundamental information-carrying functions of the nervous systems, and the mechanisms through which the various neural elements interact to produce appropriate responses to sensory experiences. Investigations include studies of sense endings, synaptic (interneural) reactions and the organization of sensory systems as well as the responses of single neural elements (cells). Many studies are on mammals, but others involve the less complicated neural structures of lower forms of life within which fundamental processes are more clearly elucidated.

Laboratory of Biophysics

This laboratory is studying the basic mechanism of activity in nerve and other excitable tissues. The principal objective is to determine the physical and chemical processes which underlie the ability of the nerve axon to transmit an information-carrying impulse. The approach combines laboratory investigations on single axons, artificial membranes, and membrane models using mathematical

analysis with the aid of computers.

Neurochemistry

The Laboratory of Neurochemistry is involved in studies of the chemical constitution of the brain and peripheral nervous system, the biochemistry of nerve activity and excitability, ion transport across membranes, and alterations of protein, lipid, and amino acid components of the brain in various diseases. These basic studies apply to a host of neurological disorders including seizure states, concussion, cerebral edema, multiple sclerosis, virus encephalitides, amyotrophic lateral sclerosis, Tay-Sachs disease and similar lipoidoses, disorders of muscle and genetically determined neurological diseases. Recent investigations have detected the essential biochemical defect in three of these devastating neurological disorders - Gaucher's disease, Niemann-Pick disease, and Fabry's disease. Newly developed techniques in this laboratory have been extensively used in diagnostic and analytical studies throughout the world.

Molecular Biology

Many disorders of the brain and sense organs are caused by abnormal biochemical reactions and/or cellular structure. New discoveries demonstrate that most of these deviations result from mutations of the genetic material, which consists of large complex molecules (DNA) that are the essence of the chromosomes in a living cell. It is important to determine the mechanisms through which the genetic material may be damaged, and the processes whereby modifications of this material lead to developmental alterations of the body. Molecular biology is concerned with an explanation of these basic biological problems in molecular terms. Working primarily with bacteria and with isolated DNA, the mutagenic and chromosomal breaking alterations of DNA produced by various chemical and physical agents are studied. The mutant organisms are then examined for their alterations in protein synthesis and function and the resultant developmental malformations are analyzed. These studies are essential to the basic understanding of the mechanisms of the inborn errors of metabolism and other genetically determined disorders.

Laboratory of Neural Control

The purpose of this laboratory is to study the mechanisms through which the nervous system responds to external stimuli and accomplishes the control of voluntary and involuntary movement. In addition, it will study ways in which the effectiveness of the normal or damaged control mechanisms can be increased by supplementation with or supplanting by artificial elements. There will be three facets to this program: research leading to development of neural control of external devices, i.e., outward information transfer; to the development of external control of the nervous system, i.e., inward information transfer; and the development of neural modeling to study the central information-processing mechanisms.

Neuro-Otology

In 1969 the Institute plans to establish a new Neuro-Otology Branch within the Intramural Program of the Institute. The Institute has developed a strong extramural program in the communicative disorders; however, one limitation of this program is that it tends towards compartmentalization because of the scarcity of trained investigators in many of the pertinent disciplines. Human communication is a multifaceted product of complex neurological processes. Consequently, the scientific evaluation of both normal and abnormal communicative processes requires a multidisciplinary approach to research which is not possible in most academic situations. A Neuro-Otology Branch will have two missions: (1) to conduct long-range research on the normal processes of the sensory, central, and efferent mechanisms which are used for human communication, and (2) to study the identification, manifestations, and amelioration of aberrations in these mechanisms.

In addition to research and training, the Neuro-Otology Branch will provide a consultation service, particularly in otolaryngology and audiology both within this Institute and the Clinical Center at Bethesda, generally.

Perinatal Physiology

Many neurological disorders such as cerebral palsy and mental retardation have their origin around or before the time of birth. To investigate the mechanisms of such damage and to study the processes of growth and development of the nervous system, the Laboratory of Perinatal Physiology utilizes a colony of rhesus monkeys, whose reproductive processes have considerable similarity to those of the human.

Within the monkeys of this colony it has proven possible to reproduce patterns of brain damage and malfunction similar to those occurring naturally in man. Studies now in progress are investigating the biochemical and physical changes associated with such brain damage in an effort to develop compensatory procedures.

The facilities of the laboratory include a main laboratory at the U. S. Public Health Service Outpatient Clinic in San Juan, Puerto Rico, and four islands on which free-ranging primate colonies are established. A new research facility, in conjunction with the National Institute of Child Health and Human Development, is being developed on the grounds of the Puerto Rico Medical Center, with completion anticipated in 1970. In addition, an experimental primate compound facility is being developed complementary to the new facility at the Medical Center.

Summary of Increases

Included in the net increase of $1,225,000 is a program increase of $875,000 which will provide for the new facility for new equipment and supplies and support for 30 new positions required for the expanded programs of intramural research. Also included is $95,000 for mandatory costs and $255,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 194 | 1,929,000 | 194 | 1,956,000 | --- | +27,000 |
| Other expenses..... | ___ | 8,261,000 | ___ | 8,250,000 | ___ | -11,000 |
| Total..... | 194 | 10,190,000 | 194 | 10,206,000 | --- | +16,000 |

Head Injury

During 1967, the planning phase of an expanded program for acute head injury research was completed and the program begun. A conference on craniocerebral trauma, sponsored by the American Neurological Association, the American Physiological Society, the Society of Neurological Surgeons, and the National Institute of Neurological Diseases and Blindness was held in Chicago in February, 1966. Clinical and basic scientists from seven countries participated in the conference and identified the following areas as warranting immediate attention: more precise information regarding incidence and prevalence; classification of injuries, and development of standards of measurement for use in clinical and research activities; prevention or reduction in incidence and severity of injuries; establishment of specialized facilities with integrated services for the treatment and investigation of head injuries - including sequential studies, rehabilitation, multidisciplinary research programs - and the participation of engineers and physical scientists in these efforts; utilization of other clinical and experimental laboratories; support of career scientists; study of data acquired by military experience; and education and dissemination of information.

The Congress, in its 1967 Report, stated that "a substantial research and training program on accidental head injuries and consequent brain damage should be launched without delay, "and designated $1.5 million for this effort, thus allowing the implementation during 1967 of some of the plans formulated at the Chicago conference.

A study of the incidence and prevalence of accidental head injury from all causes has been initiated in 1968. This pilot study is taking place in the Buffalo, New York, metropolitan area (Erie County), and involves a limited polulation. Additional research projects involving larger, smaller, and more diverse population groups are planned for 1969 using the survey design and methodology to be developed in the Buffalo study.

Six planning grants for head injury clinical research centers have been awarded, and applications for operating grants are expected in 1969.

Contracts have been let for the development of physical and mathematical models simulating the human and animal brain and skull. These models will be

used to test the mechanical forces of injury and head response for better understanding of the physical forces of head injury. This study will increase in size and scope as preliminary studies are completed.

Longitudinal studies of the effects of head injuries occurring during combat are being carried out. These studies include statistical evaluation of retrospective data on 1100 casualties from World War I. Comparative studies of data from World Wars I and II and the Korean campaign are planned. In addition pilot efforts have been undertaken, with the Department of Defense, to gather comparable data concerning the acute phase of combat head injuries incurred in Vietnam.

## Epilepsy

During the pilot phase of the Institute-supported Collaborative Study of Epilepsy, tests are being conducted at four clinical research centers to develop a protocol for collecting data on all aspects of epilepsy. When this pilot phase is completed, in 1969, the study will be broadened to include additional centers and data on a larger population of patients. Investigators hope to compile previously unavailable data concerning the natural history of epilepsy and related paroxysmal disorders, and the effectiveness of present treatment methods.

There is an urgent need for more effective anticonvulsants. Current drugs are only effective in controlling seizures in about 60 percent of epilepsy patients. With funds made available in 1967, a program of support for anticonvulsant drug development was initiated. In 1968, this program has been continued and strengthened and includes support for field trials and tests of new anticonvulsant compounds. In 1969, the Institute plans toxicity studies of new drugs having anticonvulsant properties, drug testing studies at two state hospitals, and two symposia (one on anticonvulsant drug development and one on the basic physiology of epilepsy).

Although a great deal of indirectly related but important research has been done in the past several years on the problem of the epilepsies, there has been insufficient information exchange. The publication of a journal entitled "Epilepsy Abstracts" is underway. A compilation of abstracts of articles published from 1948 through 1967 is also in preparation. The Institute hopes this effort will be complemented by the establishment of an information center to review, store, and disseminate scientific and technical information on epilepsy and on basic research studies related to this problem.

## Collaborative Perinatal Project

The objective of the Collaborative Perinatal Project is to determine those factors operating during pregnancy, labor and the early years of life which interfere with the normal, healthy development of the nervous system

and sense organs. Fourteen institutions are collaborating in gathering comprehensive data from pregnant women and their children.

Conceived and supported by NINDB, this project was initiated nine years ago in collaboration with 14 hospitals and university medical schools. Basic objectives are to learn why more than a million pregnancies in the United States each year fail to produce living children, why 126,000 babies born every year will be mentally retarded, and why thousands of others are born with neurological and other physical defects.

Institutions participating are: Buffalo Children's Hospital, Boston Lying-in Hospital, Brown University and Associated Hospitals, Charity Hospital of Louisiana at New Orleans, Children's Hospital of Philadelphia, Children's Medical Center of Boston, Columbia University, Johns Hopkins University, Medical College of Virginia, New York Medical College, Pennsylvania Hospital, University of Minnesota, University of Oregon Medical School, and University of Tennessee College of Medicine.

Data have been collected on about 60,000 pregnancies and resultant babies over the past eight years. The accumulated data pertain to infections and illnesses experienced by each mother during her pregnancy, obstetrical complications arising around the time of birth, drug intake, accidents she may have suffered, and other health circumstances. Extensive information has been collected on the social background of the parents and on the environment in which each Project child grows up. A recorded history of accidents, other traumatic experiences, and severe infections of the central nervous system occurring during the early years in the life of each child also is available. Data on the mother is nearly complete and extensive analyses are in progress in respect to obstetric aspects, perinatal mortality and events in the first year of life of the children.

Completed data are now available on several thousand children, now seven or eight years old, born to mothers during the first year of the Project. Final analysis of the entire data cannot begin until 1974 when the total information goal of the Project is complete for all study children. However, many preliminary analyses have been completed and the results made available for the improvement of maternal and child care.

Data analysis this past year has opened up a number of promising leads to further research. A number of specific studies are planned to investigate in greater depth those promising leads which have developed during the past year. Research areas to receive particular attention include the study of pathological changes in cerebral palsy, the evaluation of the role of infectious agents in neurological disorders of infancy and childhood, and the exploration of specific biochemical disturbances underlying certain nutritional and metabolic disorders of pregnancy which contribute to mental retardation.

Included in the net increase of $16,000 is an increase of $27,000 for mandatory costs offset by a decrease of $11,000 in the National Institutes of Health Management Fund.

Biometry, Epidemiology and Field Studies

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 107 | 990,000 | 107 | 1,005,000 | --- | +15,000 |
| Other expenses..... | ___ | 2,381,000 | ___ | 2,383,000 | ___ | +2,000 |
| Total..... | 107 | 3,371,000 | 107 | 3,388,000 | --- | +17,000 |

## Biometry

The Office of Biometry has been established to centralize the statistical, mathematical, and data processing services within the Institute. It brought together statisticians and mathematicians formerly assigned throughout the Institute's program areas. This organizational change has made possible a more efficient utilization of mathematicians and statisticians, and greater organizational flexibility in meeting all the Institute's program needs.

The new office has fixed or continuing responsibilities in providing consultation and assistance to the Institute's staff on mathematical and statistical matters, data processing and computer technology, and the formulation of programs wherein biometry is a vital part. Other continuing programs include the development of mathematical and statistical methodology, the collection, analysis and reporting statistical data required in the research on diseases leading to blindness, epilepsy, cerebral palsy, mental retardation, and other neurological and sensory disorders. Statistically reliable data for this research effort is obtained by collaborative agreements, contracts, or independent sources which include national and international organizations.

In addition to these continuing programs, the Office of Biometry will undertake, with the Office of Program Analysis, the study of a management information retrieval system for the Institute, the development of an ADP system for analyses of data for the Perinatal Physiology Laboratory, collaborative effort on the epidemiological research into blindness disorders, and development of mathematical systems for neurological phenomena. The above are part of the projected workload for the Office of Biometry and are illustrations of the scope of its program activities.

## Epidemiology

During 1967, a new investigation into the epidemiology of stroke was launched. Prospective studies of stroke epidemiology during 1968 and 1969 will be based on preliminary results of this study.

Studies of the epidemiology of epilepsy are underway on Guam, in Washington, D.C., and in Hagerstown, Maryland. Investigators hope through

these studies to obtain accurate information on the frequency of epilepsy, and to further delineate the relationship between epilepsy, related forms of episodic disorders, and febrile convulsions.

A study of the natural history of unilateral Parkinsonism and the effect of surgery on this condition is underway, in collaboration with the Department of Neurological Surgery, St. Barnabas Hospital, Bronx, New York, and the Brain Wave Laboratory, Massachusetts General Hospital, Boston, Massachusetts. This study will include examinations of 50 to 100 surgical cases and approximately the same number of matched control subjects.

The relationship between toxoplasmosis and astrocytoma is being explored, following the recent publication of a paper suggesting a high incidence of antibody to toxoplasmosis among patients with this form of brain tumor. Blood specimens from approximately 100 individuals with astrocytoma are being collected.

A study is underway at St. Elizabeth's Hospital, Washington, D.C., of Parkinsonism and related disorders among demented patients. Its purpose is to define these disorders and, if possible, to relate them to the Parkinsonism-dementia syndrome on Guam. Approximately 200 patients will be followed neurologically, and arrangements for neuropathologic studies will be made through resources either at St. Elizabeth's or at NINDB facilities in Bethesda, Maryland.

The significance of peripheral neuritis and other apparently unrelated disorders of the central nervous system which occur as a complication of lung cancer are being investigated. Researchers plan to study 100 cancer patients and control subjects suffering from chronic lung diseases. These investigations will be extended when analyses of findings from this pilot study are complete.

The unique resources available on the island of Guam are furthering investigations of amyotrophic lateral sclerosis (ALS) and other neurological and sensory disorders - especially Parkinsonism and dementia, which show an unusually high incidence in this isolated environment. Efforts are in progress to determine whether these disorders on Guam result from inherited predisposition of the Chomorro native of Guam, or whether they result from some environmental factor unique to that island. To test the genetic hypothesis, a large screening program for ALS in military personnel and other non-Chomorros who have lived on Guam has begun. Also, Institute researchers have developed a major follow-up study of Chomorros who have emigrated to California, to determine whether they continue to develop these disorders in that new environment. Almost 2,000 persons are under observation.

In the search for environmental factors, the investigators have made studies of the Guamanian diet, toxic substances in soil and plants, and deviations of glucose and uric acid levels in the population. A possible virus cause is being studied by inoculating into animals preparations from presumably infected brains of patients dying with ALS and Parkinsonism.

As one facet of the Institute's attack on multiple sclerosis (MS), lymphocytes from patients with MS and other degenerative neurological diseases are being studied for indications of an anti-immune process in this disorder.

These studies are being conducted at the Institute's Bethesda laboratories.

Dystonia musculorum deformans continue to be a major research target of the Section on Genetics in Epidemiology. A roster of over 400 families with this disorder has been compiled. Genetic studies so far have demonstrated that there are at least two hereditary forms of dystonia. Further efforts are aimed at delineating genetic and clinical variance within the study of families. Researchers in contact with the individuals suffering from the recessive form of dystonia are impressed by the fact that these patients are unusually bright. To test whether the gene for dystonia also confers intellectual advantage, a study is underway with the Board of Education of New York City, to compare intellectual performance of patients, normal sibs and a control group of students.

An intensive investigation of eye disease among twins is now underway and will be expanded. This study is utilizing a registry of over 450 pairs of twins, all located in the Washington, D.C. area. The examination of these identical and nonidentical twins will provide important information regarding the role of inheritance in glaucoma, myopia, and other eye disorders.

Observations of the visible blood vessels in the fundus of the eye have great value in large scale studies of cerebral arteriosclerosis. However, for such observations to be meaningful, precise methods of evaluating and measuring these vessels must be developed. The use of television scanning devices and advanced television technology presents a promising avenue of research and development in this area. Television ophthalmoscopy might also provide an improved method of studying certain disorders of the optic nerve and internal layers of the eye.

A study of malignant tumors of the eye among residents of the United States in nearing completion. These data, based on review of death certificates, will provide the first description of mortality in the United States due to specific ocular tumors.

The frequency of eye disorders has been studied among two native populations in South Pacific islands. Analyses of data during the past year show a low disease rate for some chronic disorders commonly found among Western populations. This information raises further questions regarding the influence of acculturation on the incidence of chronic diseases of the eye. For example, myopia appears to be relatively rare among simple societies.

## Slow and Latent Viruses in Neurological and Sensory Diseases

For the past several years, the Institute has been developing a program to search for viruses as a cause of such chronic neurological diseases as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinsonism and the encephalitides of childhood. The project of Slow, Latent, and Temperate Virus Infections was established in 1961-1962 as part of the Study on Child Growth and Development and Disease patterns in primitive cultures.

The Institute had long recognized the need for a laboratory to attempt the transmission of chronic and sub-acute degenerative diseases of the central nervous system of man to experimental hosts, and, in so doing, establish an infectious etiology for the specific diseases under study. The long term nature of the studies was manifest in the epidemiological and neurohistological similarities between Kuru, a disease in humans, and scrapie, a disease in sheep, which has been established to be an experimentally transmissible disease caused by an extremely small filterable agent with an associated incubation period of three to five years in natural infections, and whose expression of disease was shown to be genetically determined.

Because of the occurrence of this type of disease in wildlife, a collaborative program was established with the Bureau of Sport Fisheries and Wildlife, U.S. Department of Interior. Facilities at the Patuxent Research Center, Laurel, Maryland, were provided and augmented by the Institute's construction of a temporary primate holding facility.

The scope of the program initiated in 1962 included inoculation of several species of apes and smaller primates and small experimental animals, such as mice, guinea pigs, hamsters, rabbits and birds. The program also included study of tissue culture cell lines. Such experimentally inoculated hosts are being held for a period of five to ten years. The diseases under study are kuru, scrapie, amyotropic lateral sclerosis, the amyotrophic lateral sclerosis--Parkinsonism dementia syndrome observed in Guamanians, encephalitis, multifocal leuco-encephalopathy, Schilder's Disease, acute necrotizing leuco-encephalopathy, the hemorrhagic fevers and sub-acute sclerosing panencephalitis.

Since 1965, a total of 21 chimpanzees have experimentally developed Kuru disease. In the first transmission of the disease, eight of eight Kuru patients' brains (100% tested) have induced disease in all 12 animals inoculated, with the incubation periods ranging from 18 months to 38 months before the appearance of clinical signs. In a second transmission, eight chimpanzees (the agent has been passed in a third transmission to one chimpanzee) have developed the Kuru syndrome with a reduction of 7-8 months in incubation period.

No other experimental host system has as yet become affected, nor has disease developed in other animals following their inoculation with suspension of human tissues from patients affected with other diseases under study. The transmission of Kuru, restricted for the time to chimpanzees, is the first time a human degenerative central nervous system disease has been passed to an experimental host with perhaps a genetically influenced disease expression.

During the past year, significant data have been collected in our laboratory that provides a better understanding of the possible infectious etiology of subacute sclerosing panencephalitis. In all, 26 cases from the United States and 35 cases from several central European countries have been studied serologically. In every instance these cases have demonstrated a hyperimmune antibody status to measles virus. In several cases myxovirus-like virus particles have been observed by electron microscopic examination of the intra nuclear inclusion bodies found in surgical biopsy and autopsied brain specimens. Intensive attempts are being made to experimentally transmit the disease to myxovirus antibody free primates, ferrets, other mammalian hosts, and to cell cultures.

These developments have required an expansion in the number of experimental animals to be inoculated. They have also required an increase in the number of

species of apes, monkeys, and domestic animals to broaden the host susceptibility range and to find more readily available and substantially less expensive animals than the chimpanzee. There is a need to enlarge and improve laboratory and animal holding facilities to insure protection of individual investigators and technicians, and long term program animals in well-controlled isolation. In order to move rapidly in the follow up of the program developments, the Institute is developing an increase in animal holding space, largely through the use of contracts.

Information Centers

The Institute has developed a National Neurological Information Network to facilitate the prompt exchange of information within the medical and scientific community through the establishment of research and information centers in four universities having outstanding library facilities. The network is coordinated by the Office of Program Analysis, NINDB, and operates in close collaboration with the National Library of Medicine. It is engaged in a review of scientific reports, indexing for the MEDLARS system, publication of bibliographies, special searches, symposia, and a review of articles on topics of special interest.

Included in the net increase of $17,000 is an increase of $15,000 for mandatory costs and an increase of $2,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Training Activities

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 3 | 45,000 | 3 | 46,000 | --- | +1,000 |
| Other expenses..... | | 28,000 | | 28,000 | | |
| Total..... | 3 | 73,000 | 3 | 74,000 | --- | +1,000 |

This activity supports the Institute's training programs for professional, technical, administrative, and clerical personnel, including job-related training at both government and non-government facilities.

The primary objective of the program is to train scientists in particular skills which are needed to carry on various Institute research projects. Long term training is provided by the establishment of agreements and contracts with appropriate schools or institutions.

Program plans provide for training in otolaryngology, neurology epidemiology, and neurosurgery. A net increase of $1,000 is included for mandatory costs in 1969.

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 106 | 982,000 | 113 | 1,023,000 | +7 | +41,000 |
| Other expenses..... | | 1,436,000 | | 1,476,000 | | +40,000 |
| Total..... | 106 | 2,418,000 | 113 | 2,499,000 | +7 | +81,000 |

Extramural Programs

Within the extramural program office of this activity, all grants and awards, such as research grants, program project grants, training grants and fellowship awards are programmed, examined, processed and continually followed up by the professional, administrative, and clerical staff. Formal reviews are performed by several organized and ad hoc bodies of non-governmental authorities in the health and science fields, including the National Advisory Council on Neurological Diseases and Blindness, training review committees and study sections of this Institute and Division of Research Grants, National Institutes of Health. The magnitude of the managerial and review processes in terms of number of grants, dollar volume, and programming complexities are imposing greater demands in terms of data for and advice on programming. Two mechanisms are being resorted to more frequently: advisory groups or task forces expert in critical fields and gradual introduction of greater sophistication and capabilities in the retrieval and analysis of data regarding grants and programming. Both these types of activities are funded out of the Review and Approval activity, and the latter is directly coordinated and interdigitated with activities of the program analysis function in the Office of the Director, NINDB. During 1968, steps will be taken to concentrate the major institute facilities for information and data storage and retrieval in the extramural program office, where the vast majority of the data originates, and to design the facility so that it can be tied into central NIH computing facilities for analytical studies in the future.

Included in the net increase of $81,000 is a program increase of $25,000 and 7 positions for additional requirements in the review and analysis of the grant programs of the Institute. Also included is an increase of $16,000 for mandatory costs, and an increase of $40,000 for centrally furnished services from the "National Institutes of Health Management Fund".

Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 32 | 311,000 | 32 | 316,000 | --- | +5,000 |
| Other expenses..... | --- | 364,000 | --- | 404,000 | --- | +40,000 |
| Total..... | 32 | 675,000 | 32 | 720,000 | --- | +45,000 |

This activity supports the professional direction and the administrative and clerical services required for the Institute's programs and activities. The Office of the Director provides for the centralized supervision, coordination and review of these programs, as well as for the direction of the administrative functions of finance, personnel, supply, travel, space utilization and management analysis. Also included as part of the Office of the Director is the Office of Program Analysis, which is responsible for developing for the Institute a computerized central management information system, as well as workshops, training programs and general scientific information activities.

Included in the net increase of $45,000 is a program increase of $19,000 which will provide services support of the administrative staff in the Office of the Director. Also included is $5,000 for mandatory costs and $21,000 for centrally furnished services from the "National Institutes of Health Management Fund."

WEDNESDAY, MARCH 20, 1968.

# NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

## WITNESSES

DR. DORLAND J. DAVIS, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. JOHN R. SEAL, DIRECTOR, INTRAMURAL RESEARCH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
WALTER H. MAGRUDER, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
MARTIN J. FULLER, BUDGET OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimated | 1969 estimated |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 5,902 | 6,136 | 6,371 |
| Positions other than permanent | 52 | 53 | 53 |
| Other personnel compensation | 134 | 147 | 149 |
| Total personnel compensation | 6,088 | 6,336 | 6,573 |
| Personnel benefits | 660 | 780 | 798 |
| Travel and transportation of persons | 222 | 300 | 300 |
| Transportation of things | 73 | 75 | 75 |
| Rent, communications, and utilities | 228 | 230 | 230 |
| Printing and reproduction | 13 | 45 | 45 |
| Other services | 1,176 | 1,046 | 1,101 |
| Project contracts | 9,606 | 10,641 | 11,800 |
| Payments to "National Institutes of Health management fund" | 4,976 | 5,428 | 5,331 |
| Supplies and materials | 1,717 | 2,207 | 2,200 |
| Equipment | 628 | 650 | 650 |
| Grants, subsidies, and contributions | 61,336 | 65,782 | 69,477 |
| Subtotal | 86,723 | 93,520 | 98,580 |
| Quarters and subsistence charges | −18 | −18 | −18 |
| Total obligations | 86,705 | 93,502 | 98,562 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 729 | 741 | 759 |
| Full-time equivalent of other positions | 6 | 6 | 6 |
| Average number of all employees | 695 | 691 | 705 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 48,973 | 52,264 | 55,627 |
| (b) Fellowships | 3,446 | 4,267 | 4,362 |
| (c) Training | 8,916 | 9,251 | 9,488 |
| Total grants | 61,335 | 65,782 | 69,477 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 13,003 | 14,852 | 15,142 |
| (b) Collaborative research and development | 7,969 | 11,023 | 12,034 |
| (c) Review and approval of grants | 1,337 | 1,479 | 1,504 |
| (d) Program direction | 343 | 366 | 405 |
| Total direct operations | 22,652 | 27,720 | 29,085 |
| Total program costs, funded [1] | 83,987 | 93,502 | 98,562 |
| Change in selected resources [2] | 2,718 | | |
| Total obligations | 86,705 | 93,502 | 98,562 |
| Financing: | | | |
| Comparative transfers to other accounts | 2,893 | | |
| Unobligated balance lapsing | 1,060 | 920 | |
| New obligational authority | 90,658 | 94,422 | 98,562 |
| New obligational authority: | | | |
| Appropriation | 90,670 | 94,422 | 98,562 |
| Transferred to other accounts | −12 | | |
| Appropriation (adjusted) | 90,658 | 94,422 | 98,562 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 86,705 | 93,502 | 98,562 |
| Receipts and other offsets (items 11–17) | 2,893 | | |
| Obligations affecting expenditures | 89,598 | 93,502 | 98,562 |
| Obligated balance, start of year | 50,606 | 56,489 | 72,812 |
| Obligated balance, end of year | −56,489 | −72,812 | −91,374 |
| Adjustments in expired accounts | −1,449 | | |
| Expenditures | 82,266 | 77,179 | 80,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 37,711 | 35,379 | 36,000 |
| Out of prior authorizations | 44,555 | 41,800 | 44,000 |

[1] Includes capital outlay as follows: 1967, $320,000; 1968, $650,000; 1969, $650,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $7,848,000; 1967, $10,566,000; 1968, $10,566,000; 1969, $10,566,000.

Mr. FLOOD. Now we have the National Institute of Allergy and Infectious Diseases, and the presentation will be made by Dr. Dorland J. Davis, the Director.

We will insert at this point in the record the biographical sketch of Dr. Davis.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

(The sketch follows:)

BIOGRAPHICAL SKETCH

Name: Dorland J. Davis, M.D.

Position: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Birthplace and date: Chicago, Ill., July 2, 1911.

Education: 1933, University of Illinois, B.S.; 1937, Johns Hopkins University, M.D.; 1940, Johns Hopkins University, Dr. P.H. (epidemiology); 1949, certified by the American Board of Preventive Medicine and Public Health.

Experience: 1964 to present, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; 1956, Associate Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; 1954, Chief, Laboratory of Infectious Diseases, National Microbiological Institute (now National Institute of Allergy and Infectious Diseases) NIH; and 1939

to 1954, commissioned officer on duty at National Institutes of Health (1943–44 on duty in North Africa for the State Department).

Association memberships: Fellow, American Academy of Microbiology; fellow, American College of Preventive Medicine; American Association of Immunologists; American Epidemiological Society; American Society of Tropical Medicine and Hygiene; World Health Organization Panel on Virus Diseases; board of directors, Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.; and member, National Research Council, Division of Medical Sciences (executive committee).

Special awards, citations, or publications: Edward Rhodes Stitt Award, Association of Military Surgeons of the United States, 1955; Phi Beta Kappa; Meritorious Service Medal, Commissioned Corps, U.S. Public Health Service, 1967; publication of 43 papers on infectious diseases.

## General Statement

Dr. Davis. Mr. Chairman and members of the committee, medical science can claim many victories against disease, but man is continually threatened by infectious agents—whether they be viruses, bacteria, fungi, or parasites. Casualties remain high. Allergic and infectious diseases together rank third as the cause of death, taking the lives of nearly 110,000 Americans each year. Of these, respiratory infections—including influenza and pneumonia—account for about 70,000 deaths; an estimated 20 mililon Americans suffer from allergies.

It is increasingly apparent that two disciplines basic to this Institute have a profound impact on all biomedical research: Immunology, a study of the body's protective reaction, and microbiology. Their impact will continue to increase. To illustrate, I will highlight three significant areas of Institute research; one from the field of immunology, and two from microbiology.

### TRANSPLANTATION IMMUNOLOGY

Today, organ transplantation is surgically possible. This is evident by recent dramatic news reports of the transfer of hearts from persons recently dead to living recipients. Of the 1,600 persons who have received kidney transplants since 1954, more than half are still alive. Within the past year, a surgeon in Colorado has transplanted livers in five children with encouraging results.

The primary obstacle still to be overcome is the immune response—the body's tendency to mobilize specialized forces (white cells and blood substances called antibodies) to destroy the foreign tissue. This is the same response the body makes to disease-causing microbes. Two keys to successful organ transplantation are (1) tissue typing techniques and (2) suppression of antibody production.

Scientists have identified a relatively small number of substances in the body's tissue cells which are important in determining acceptance or rejection of a transplant. Tissue typing techniques—similar in concept to the familiar red-blood-cell matching principles now used routinely for blood transfusions—have been developed by investigators supported by this Institute since 1965.

### FRACTIONATION OF BLOOD

Mr. Flood. Does the breaking down of the blood into fractions contribute in any way?

Dr. DAVIS. Yes. This has been a very important development, and, of course, it goes back some years. So that now we are able to identify the various kinds of substances in the blood, whether globulins or albumin, and particularly what kind of globulins are effective in reacting against certain infections.

And we can specify quite clearly now the different kinds of globulin fractions.

LIVER TRANSPLANTS

Mr. FLOOD. You say "Within the past year a surgeon in Colorado has transplanted livers of five children with encouraging results." Just how successful were these transplants?

Dr. DAVIS. One child is still living 5 months after transplantation. The others have unfortunately died, two of them actually within the last 2 weeks.

Mr. FLOOD. What you mean is "Starting from nothing, this is pretty good."

Dr. DAVIS. Considering that the liver is a single organ, meaning that we have only one, and the surgical complications of transplanting such a complex organ, I think this is making progress. Actually, this work had gone on in experimental animals for several years, and those results encouraged the surgeon to move to humans.

HEART TRANSPLANTS

Mr. FLOOD. Are you aware of Dr. Hufnagel's project—he is a distinguished surgeon at Georgetown University here—with reference to heart transplants. I am speaking not so much of the transplant itself, which apparently is not much of a trick if you are a first-class surgeon. Of course, I am not underestimating the significance of that achievement at all. But I am speaking primarily of the post operative rejection problem. He injects into the heart of a calf something that would diminish the rejection process. You could then transplant the calf's heart into the human and a great deal at least of the rejection problem has been anticipated and met.

Dr. DAVIS. Yes. This is the principle of tolerance. Tolerance of foreign proteins.

Mr. FLOOD. Is it within the realm of reason to put a calf's heart in a human being?

Dr. DAVIS. It has been speculated that animal hearts could be put into humans, but one would have to modify, as you have indicated, the immunological tolerance to the animal heart so that a rejection reaction would not occur. That is what Dr. Hufnagel is trying to get at. This is a very imaginative idea and certainly should be pursued. We need to have much more research on the basic problems of rejection.

Mr. FLOOD. Dr. Hufnagel is no amateur.

Dr. DAVIS. No.

Early tests indicate that proper matching between donors and recipients before organ transplantation will increase the likelihood of a successful transplant.

Even with tissue matching, the rejection activity of the recipient cannot be completely eliminated. Various immunosuppressive methods—including X-ray, drugs, and biological preparations—are being employed to reduce rejection.

Existing drugs have two disadvantages: they are toxic to the tissues and tend to suppress the body's normal protective reaction to infection. One biological preparation known as antilymphocyte serum—which is obtained from horses immunized with human white blood cells—acts by preventing the formation of antibodies that cause organ rejection. Institute-supported scientists are conducting animal studies of immunosuppressive methods for the better control of rejection.

### RESPIRATORY DISEASE VACCINE

A major effort of the Institute is directed toward developing vaccines against virus infections. One outstanding accomplishment has been the development of an oral vaccine against Adenovirus type 4—a common disease among military recruits. The Army used this vaccine last year in 12 camps with an estimated 44-percent reduction in respiratory disease and as much as $18 million saved in hospitalization costs and training time.

The Institute is extending its efforts to develop a vaccine against pneumococcal pneumonia—a bacterial disease responsible for as many as 40,000 deaths a year and an estimated 300,000 hospitalized cases. The highest mortality from this disease is in the elderly and chronically ill patient who often develops an overwhelming infection before antibiotics can take effect. A successful vaccine, by preventing disease, would reduce some of the staggering costs of hospitalization and prolong useful lives.

### RUBELLA (GERMAN MEASLES) VACCINE

Since 1966—when the Congress provided NIAID with additional funds for coordinating the development of a rubella vaccine—NIH scientists in the Division of Biologics Standards (1) have developed an attenuated rubella virus strain (HPV–77) which appears to confer immunity without transmitting the infection to unvaccinated contacts and (2) have perfected a method of measuring rubella immunity through a simple, yet sensitive and reliable test.

Mr. FLOOD. Which appears to confer immunity?

Dr. DAVIS. Yes.

Mr. FLOOD. Is not immunity an absolute term? How do you appear to? Either you do or you do not?

Dr. DAVIS. The real test is whether these people have immunity against the natural disease under natural conditions. And the number of people, adults and children, vaccinated so far is something in the order of 500 or 600. So only a few of those have actually had a chance to be exposed to the natural disease and those few seemed to be immune.

Mr. FLOOD. That is not very many people, is it?

Dr. DAVIS. No, but this vaccine is in the process of being developed and tested and there just has not been time to make all of these evaluations.

Actually, one of the major efforts in the next year will be to extend these evaluation studies to a number of different populations and we hope by this time next year we will be able to report that they have been used in several thousands of individuals.

Mr. FLOOD. You say you have already perfected a method of measuring the immunity through a very simple, very reliable test?

Dr. DAVIS. Yes, sir.

Mr. FLOOD. That is a pretty flat statement. Is it that precise and exact and positive?

Dr. DAVIS. Yes. This is a very precise test which has been used for about a year now. It was worked out in animals, in monkeys, and now it is being extended into humans. Of course it is being used in adults to determine, for instance, the proportion of individuals in a given population who may be immune to the disease.

I think it is a good test which has about the same reliability as our other biological tests. But this measures the antibodies in the blood, and such a measurement is a different thing really from determining whether these people are fully protected against the natural infection, something that can be determined only by actual experience.

Mr. FLOOD. Go ahead.

Dr. DAVIS. Scientists in pharmaceutical companies—both under NIAID contract and in independent projects—have produced sufficient quantities and varieties of vaccines to test in limited groups. Evaluation centers are ready for field trials. We are hopeful that rubella vaccines will be available for mass vaccination before the next rubella epidemic which is predicted for the early 1970's.

Mr. FLOOD. Who would you vaccinate?

Dr. DAVIS. We would recommend vaccinating children first. The greatest danger, of course, is to the pregnant woman, and we would hope to have devised a public health practice to insure that pregnant women or women likely to become pregnant will be vaccinated. Vaccination could best be done during childhood, but if that is not possible, a special effort ought to be made in young women before possibility of pregnancy.

Mr. FLOOD. Is one vaccination enough?

Dr. DAVIS. We do not know yet because the first vaccinations were performed only about 2 years ago.

Mr. FLOOD. Why would you vaccinate all of these children then? Why would you have a mass immunization of children?

Dr. DAVIS. Vaccines of this type, that is, live-attenuated vaccine, generally confer permanent or long-term immunity, as for example measles vaccine. So that we would hope and expect that one vaccination would do it. Perhaps as we get into an evaluation of duration of immunity, we will find that maybe a second or booster vaccination would be necessary later on. But the questions you ask are those which will have to be worked out by evaluations lasting over a period of several years.

The fact is that about 85 percent of young adults in the United States have antibodies in their blood, and presumably are immune. Therefore, one would have to find that 15 percent of adults, in order to vaccinate them, or else vaccinate all adults or youngsters.

Mr. FLOOD. Could this be an oral vaccine?

Dr. DAVIS. It might be. There have been a number of trials of a rubella oral vaccine. So far these have not been successful. The only successful administration so far has been by injection.

Mr. FLOOD. I suppose it could be administered by this piece of hardware you use for the regular measles, could it not?

Dr. DAVIS. It might be.

Mr. FLOOD. We will place your special report on rubella in the record.

(The report follows:)

SPECIAL REPORT: RUBELLA

Approximately every 7 to 10 years, rubella (or German measles) reaches epidemic proportions in the United States. In children, the virus-borne disease usually causes only mild symptoms. But to a woman exposed to rubella in early pregnancy—especially if she is the one adult in five who has not had rubella—the ailment creates understandable apprehension. Not for herself, but for her unborn child. For if the mother contracts rubella in the first 3 months of pregnancy, there is the increased risk that her child will (1) never reach full term, (2) die soon after birth, or (3) be born crippled by such defects as mental retardation, heart disease, cataracts, glaucoma, or deafness.

The tragedy of rubella was emphasized during 1964–65, when an epidemic in the United States left in its wake an estimated 30,000 abnormal pregnancies. Clinicians across the country continue to report on the extent of damage: infants born with one or more defects who later develop others; laboratory studies verifying a variety of blood, liver, bone, pulmonary, and vascular abnormalities; and at least half of the children suffering some degree of hearing loss.

RUBELLA MILDLY CONTAGIOUS

Rubella is less contagious than such ailments as rubeola (common measles) and chickenpox. It is caused by a virus spread by droplet spray from the nose and throat and, like measles, may be air-borne for short distances. Its symptoms: a slight headache, fever, some muscular pain, and swelling of the neck preceding a cough, nasal congestion, and a pink rash which usually lasts about 3 days.

The disease was first linked to birth defects in 1941, by the late Dr. Norman Gregg, an Australian opthalmologist who traced an unprecedented number of cataracts in babies to a rubella epidemic in 1940. Later it was learned that rubella contracted during the first 12 weeks of pregnancy causes about 20 percent of the stillbirths and congenital abnormalities. Also, some babies show no symptoms of rubella at birth; however, they may harbor the virus for months or years, passing on the disease to others, including women in early pregnancy.

EARLY RESEARCH

It was only in 1962, that two groups of investigators—at Harvard University and Walter Reed Army Institute of Research—reported simultaneously the isolation of the rubella virus and its growth in cell cultures. Since these achievements, investigators have been attempting to develop vaccines using both killed and live rubella virus. (A killed virus vaccine is produced by growing the virus in a tissue culture and then inactivating—or killing—the material by chemical or physical means. A live virus vaccine is made by repeatedly passing the virus through tissue cells until it is attenuated (weakened) to the point where it can produce immunity without causing the disease. Examples of these two types are those developed against polio: the Salk vaccine is a killed virus vaccine, the Sabin vaccine a live vaccine.)

In early experiments, both killed and live preparations of rubella virus posed complex problems. The killed virus vaccine lost much of its immunity-producing ability during inactivation. And many of the volunteers vaccinated with live virus vaccines developed rubella and transmitted the infection to those around them.

COLLABORATIVE EFFORT UNDERTAKEN

It soon became apparent that an intensified, coordinated program was needed to develop a rubella vaccine, and this challenging task was assigned by the Congress to the National Institute of Allergy and Infectious Diseases. The Institute employed the approach that has worked well in the effort to develop respiratory virus vaccines, utilizing its collaborative research program to coordinate the efforts of Government, industrial organizations, and universities in a massive cooperative voluntary partnership. Joined in the effort are seven of the Nation's leading pharmaceutical companies, three private research laboratories, six uni-

versity medical centers and related facilities in the Bethesda laboratories of the National Institute of Neurological Diseases and Blindness, the Division of Biologics Standards, and the National Institute of Allergy and Infectious Diseases.

THE FIRST PROMISING EXPERIMENTAL VACCINE

The year 1966 may well prove to be most important in terms of rubella vaccine accomplishments. For it was in 1966, that two scientists in the Division of Biologics Standards (DBS) succeeded in producing a live attenuated rubella virus vaccine. Known as HPV–77, it was attained by passage of the live rubella virus through green monkey kidney cell cultures 77 times to a point where it was sufficiently potent to stimulate antibody production but still not cause the disease.

To the DBS scientists also goes the credit for perfecting a method of measuring rubella immunity through a test known as hemagglutination-inhibition (H-I test). Because of the test's simplicity, speed, sensitivity, and reliability, the stage was set for more rapid and effective clinical evaluation studies than had formerly been possible.

Since 1966, vaccines prepared from HPV–77 vaccine or its derivatives, have now been administered to approximately 550 persons. None of these individuals experienced vaccine-associated reactions; more than 90 percent developed protective immunity. Continued observation of the first groups of children vaccinated 2 years ago indicates that the immunity conferred by the attenuated virus will be of long duration. Thus far, the vaccine appears safe as well as effective.

During the past year, scientists contributing to this collaborative effort have had the opportunity to evaluate the vaccine produced in a variety of tissue cultures and to assess certain factors which, at the onset, gave rise to some concern. For example, one problem was the tendency of all live attenuated rubella vaccines to shed the virus from the nose and throat of those inoculated. This raised the question of whether the shedding might create difficulties in mass immunization if susceptible pregnant women were exposed. However, recent studies involving a number of animals and a lesser number of women ( whose pregnancies were to be interrupted for medical reasons) indicate that the attenuated rubella virus (HPV–77) is not sufficiently virulent to pass through the placenta to the embryonic child.

Investigators and collaborating groups during the past year have sought the answers to several questions important to the development of the vaccine. These questions involved (1) determining the optimum degree of attenuation for a virus strain destined for use in vaccine production, (2) evaluating the characteristics of experimental rubella vaccines produced in various types of tissue cultures, and (3) ensuring the maximal practical application of the new H-I blood test in detecting immunity and determining protective antibody response in vaccines.

THE FUTURE

During the coming months, all members of the collaborating rubella vaccine team will be involved in some aspect of this massive program. Some will be working to produce sufficient quantities and varieties of vaccine to meet licensing specifications. Others will be engrossed in activating evaluation centers. Still others will coordinate progressively larger rubella vaccine field trials. With the continued spirit of cooperation, and capitalizing on the research achievements of the past year, it is anticipated that the advanced stages of rubella vaccine development should proceed rapidly.

Although the numerous steps in a vaccine production program often make it impossible to maintain a set time schedule, there is great hope among the investigators that rubella vaccines could be available for mass vaccination well before the next rubella epidemic which is expected in the early 1970's.

When a vaccine is ready to stand off the onslaught of the next epidemic, the credit will be shared by a cross-section of Americans . . . those who performed the basic research in Government, pharmaceutical, and university laboratories . . . those who produced a safe and effective vaccine . . . those who volunteered for experimental vaccination and those who administered the vaccine . . . and those farsighted members of Congress who encouraged this effort.

Dr. DAVIS. These areas represent only three of the opportunities we at NIAID have to contribute to the improvement of our Nation's health. We welcome these opportunities, and we have strong convic-

tions that the support our Institute has enjoyed in the past will continue to pay dividends to our fellow Americans in the years to come.

The 1969 request for the National Institute of Allergy and Infectious Diseases is $98,562,000, including $500,000 for the Gorgas Memorial Laboratory, an increase of $5,060,000 over the operating level of $93,502,000 for 1968. The 1969 request provides an increase of $3,363,000 for research grants; $95,000 for fellowships; $237,000 for training grants; $290,000 for laboratory and clinical research; $1,011,000 for collaborative research and development; $25,000 for review and approval of grants, and $39,000 for program direction.

I shall be happy to answer any questions.

Mr. Chairman, I have copies of three other special reports here which have been sent to you. These are on organ transplantation, the respiratory virus vaccine, emphysema and chronic bronchitis.

(The reports follow:)

## Organ Transplants

For many years, immunology has been concerned with the body's response to infectious disease agents. More recently, the field has been broadened to include investigations of the host response to transplanted tissues. Immunologists have contributed the knowledge necessary for the first major steps toward realization of one of man's favorite dreams—the ability to replace failing organs.

They have learned that body tissues posses certain substances which function as antigens. These antigens—present in a donor's kidney, liver, or heart, for example—are recognized as "foreign" by the body of the transplant recipient. The body, in response, produces antibodies and specialized, defensive white blood cells which eventually overwhelm the new organ. The transplanted organ ceases to function, degenerates and dies, rejected by the body it was intended to help.

Delayed hypersensitivity is the immunological mechanism generally believed to underlie graft rejection, as well as many of the autoimmune (or self-destroying) diseases. As yet, relatively little is known of the biochemistry of this mechanism, the principles of controlling it, or even its natural biological and evolutionary functions.

Nevertheless, wth the aid of antirejection techniques such as radiation and drug therapy—which lower the body's response to these or any foreign antigens—and with the surgical skills which have been refined to permit the actual transplant operation, scientists can generally force the body to accept a new organ—at least temporarily. Repeatedly, surgeons have shown that organ transplantation is feasible: the first human heart transplant patient lived for 18 days last December before infection took his life; last year, several young recipients of liver transplants survived longer than previous recipients; and over half the more than 1,600 recipients of kidney transplants since 1954 are still alive today.

Most transplant operations have involved the kidney, and the organ-survival rate continues to climb as techniques and skills become more sophisticated. At present, almost 70 percent of the kidneys transplanted from living, related donors (and 50 percent of those from nonrelated donors) continue functioning for at least 2 years. And if one kidney transplant is rejected, the patient can be maintained on the artificial kidney (dialysis) until another becomes available, further increasing the chances for success.

But the immune response—the body's ultimate rejection of the lifesaving graft—still prevents transplantation from becoming a permanent solution for any patients except identical twins, whose tissues have a common genetic origin and therefore do not react against one another.

The twin goals of transplantation immunology are: understanding the mechanisms of the immune response and finding ways to minimize the problem of organ rejection. Three groups of scientists work toward these ends under NIAID guidance—intramural scientists in its Bethesda, Md., laboratories; some 26 contractors cooperating under its collaborative program in transplantation immunology to achieve specific goals; and some 55 research groups at universities and medical centers across the country supported by Institute grants.

### TISSUE TYPING AND MATCHING

Though technological skills have outstripped immunological knowledge, much has been learned. Scientists now know, for example, that some of the antigens which trigger the immune response are more potent than others in evoking the body's defenses. They have identified a relatively small number of such stronger antigens (known as histocompatibility antigens) in the body's white blood cells.

They have developed techniques for typing individuals according to their white-cell antigens, in much the way red-cell typing for blood transfusions has long been done. Under the Institute's collaborative program, five medical institutions—in Los Angeles, Seattle, New York (two), and Boston—now operate typing facilities for hospitals in those areas, where kidney transplant operations are performed. Scientists at these institutions are testing the value of the current typing techniques in maching pairs of potential donors and recipients of kidneys. The aim is to select those pairs whose strong antigens are most nearly alike—the donor kidney least likely to be rejected by the recipient body. Retrospective testing of these experimental techniques has already indicated that proper matching before transplantation smooths the course of the transplant and reduces the immune response.

At the Los Angeles facility, computers aid scientists in speeding the matching process. A computer stores typing data on the kidney disease patients in that area, who are presently kept alive by dialysis. When a donor organ becomes available and is typed—a process requiring about 3 to 4 hours with present techniques—the computer can quickly identify the prospective recipient most likely to be compatible; that is, a "good match" for the new organ. Such a data retrieval system is also used by the recently formed Transplantation Society to store information on persons who have offered their kidneys for transplantation when they die.

All five institutions seek to coordinate established kidney transplantation and dialysis programs so that large populations of previously typed potential recipients, now on dialysis, can be matched to potential donors.

Through the NIAIDS's two serum banks—in the United States and Holland—transplantation teams all over the world have access to typing materials developed under the contract program. An international workshop on histocompatibility sponsored by the Institute last year documented the great improvement in the quality of typing antisera (serum containing antibodies to the known antigens). The workshop also revealed the continuing refinement of typing and matching techniques and yielded valuable genetic information which increased understanding of the inheritance of histocompatibility antigens.

This year, as a direct result of the workshop and subsequent meetings, a proposed effort in cooperation with the World Health Organization may result in a coordinated nomenclature system. This could prove as valuable to histocompatibility typing as the ABO blood grouping system has been to red-cell typing and blood transfusion.

The Institute's contractors are refining typing techniques; characterizing, storing, and distributing the reagents needed for tissue typing, and working to isolate, purify, and characterize all of the antigens which play a part in the immune response.

### SUPPRESSING THE REJECTION RESPONSE

Even the most sophisticated matching techniques probably cannot eliminate all conflict between tissues. Also, in the actual practice of transplantation, the best available organ may not always be the best antigenic match. Thus, advances in methods of suppressing the immune response are of great importance.

Steroids, antimetabolites or other immunosuppressive drugs, and radiation are now used to persuade the body to accept new tissues. All of these methods depress the body's immune capabilities, thereby reducing—and sometimes eliminating entirely—its ability to respond to infection from any source. These immunosuppressives are toxic to the tissues and may have undesirable side effects on the patient. They must be continued indefinitely to maintain the body's acceptance of the graft. A major problem for the physician is determining the minimal dosage which will aid the patient in his fight to keep the new organ without lowering his resistance to infection. Although there has been reasonable success in maintaining active, healthy patients with drugs after they pass the critical 18-month period during which kidney rejection is most likely, the effects of long-term use of these potent drugs remain unknown.

Attention has increasingly turned to biologic immunosuppressives, such as antilymphocyte serum (ALS), and more recently to a purified portion of ALS called antilymphocytic globulin or ALG. Essentially, such serum (produced by animals in response to injection with human white cells) prevents the formation of antibodies that cause rejection. In a sense, ALS and ALG are decoys, diverting the attention of the body's first line of resistance from its attack on the transplant. Evidence indicates that the combined use of tissue typing and ALG significantly improves the chances for continued function of a kidney or liver transplant, particularly in transplants between close relatives.

The antilymphocyte serum, however, shares the basic disadvantage of all immunosuppressives so far developed—it is essentially foreign to the body. Grantee research recently has raised the possibility of isolating normal constituents of human tissue which may regulate the immune response itself. In the future, such components may be extracted and purified for use as a selective depressor of the body's defense.

The ultimate goal of transplantation immunology is the induction of immunological tolerance only to the antigens of the donor. Recently intramural scientists have developed the techniques for isolation, identification, and characterization of transplantation antigens from the tissues. Work so far has been with guinea pigs, but purified material suitable for analyzing the composition and structure of these highly specific antigens can be obtained. The findings, hopefully, will be applicable to human tissues as well.

Extension of this work, together with the anticipated development of methods for growing in tissue culture the specific white blood cells containing the principal transplantation antigens of man, could provide a valuable immunosuppressive tool. Success with these two developments may make possible production of these antigens in sufficient quantity for use in inducing tolerance to a specific organ.

Under its special emphasis program, the Institute will sponsor a conference this year on progress in the study of immunological tolerance. This meeting will bring together workers in the field and hopefully speed effective clinical application of their research.

### ORGAN PRESERVATION

As the techniques and skills develop for transplanting organs and inducing the body to accept them for longer periods, the need grows for new ways to preserve and store available organs until they can be used to best advantages. Because there is a potential for filling all of the kidney transplantation requirements (estimated at 6,000 to 10,000 a year), the Institute directs its preservation studies toward extending the viability of that organ for several days. Now it remains useful for only about 4 to 6 hours after removal.

Freezing techniques are being studied in an effort to eliminate the tissue damage caused by this method of preservation. Some scientists also are attempting to assess the extent of cellular and organ damage after subjection to low temperatures. Others are seeking a kidney perfusion system which would simulate the conditions under which the organ normally operates inside the body.

### NEW PROBLEMS AND NEW KNOWLEDGE

As transplants become more frequent, the concern grows over their long-term results—such as the loss of the transplanted organ through recurrence of the original disease and damaged produced by immunosuppressive therapy. Institute-supported studies are concerned with long-term followup of recipients of organ transplants. As transplants become more frequent, the knowledge acquired may also pay dividends—not only in prolonging productive life and successfully treating kidney disease, but also in providing the knowledge needed for the treatment of diseases of other organs. Successful kidney transplantation, together with the advances being made in immunology itself, may furnish the opportunity to learn the causes of kidney disease, thus leading to the next step—prevention.

## Respiratory Vaccine Development

During fiscal year 1965–66, economic loss to the Nation from absenteeism caused by acute respiratory diseases was estimated at almost $3 billion. Because widespread epidemics of influenza and "influenza-like" illnesses occured in the winter of 1967–68, the economic loss may be even larger this year. Deaths

from these diseases, even in normal years, claims about 70,000 persons, including 10,000 infants.

What are the acute upper respiratory diseases? The common cold, caused by the rhinoviruses, is the most frequent problem—about 500 million colds are suffered each year in the United States—or roughly 2½ colds for every person. One Institute contractor's study revealed that 10–20 percent of all absenteeism was due to rhinovirus infections.

Pneumonia—occurring with much less frequency (about 2 million cases a year)—accounts for a high percentage of the deaths due to upper respiratory infections and, indeed, to infectious diseases as a whole. Viruses such as influenza, parainfluenza, resipratory syncytial, and adenoviruses, as well as *Mycoplasma pneumoniae*, an organism which is neither bacterial nor viral, but has characteristics of both, and pneumococcal bacteria are the chief causes of these illnesses. Streptococcal bacterial infections produce severe sore throats and high fever, but are much more important for their after-effects. If untreated or treated inadequately, about 3 percent of streptococcal infections will result in the later development of rheumatic fever or the kidney disease, glomerulonephritis.

New causes of acute upper respiratory disease are constantly coming to light. In 1967 a new class of human viruses, named IBV-like viruses for their resemblance to the infectious bronchitis virus of birds, was discovered during common cold studies in the intramural laboratories and by a grantee (Hamre at the University of Chicago) and found to be capable of producing colds.

Efforts are being made to combat the viral respiratory diseases with so-called antiviral substances—chemicals which act against viruses as antibiotics act against bacteria—but these drugs are still in the early stages of research. Vaccines to prevent the development of these viral diseases as well as *M. pneumoniae* are presently the best immediate hope for their control.

Pneumococcal and streptococcal infections can be treated with penicillin, but they must be treated promptly and adequately. The abrupt onset of severe pneumococcal pneumonia, especially in a person over 50, or one with other ailments, may result in death before adequate penicillin treatment can be instituted. Streptococcal infection, on the other hand, may be mild enough to go untreated, or the patient may be treated with an inadequate drug, or for too short a time to prevent later development of rheumatic fever or severe kidney disease. Vaccines against these organisms could, therefore, prevent a sizable number of deaths and hospitalized illnesses from pneumonia and cut disability due to rheumatic fever and chronic kidney disease markedly.

### COLLABORATIVE RESEARCH PROGRAM

The development of vaccines against acute upper respiratory diseases is the responsibility of the Institute's collaborative research program. This program seeks, through the mechanism of contract support, to translate research findings as quickly as possible into socially important technology for promoting the health of the Nation. The respiratory vaccine development branch of the collaborative research program is charged with the planning, direction, and coordination of this complex program. Advice and counsel is provided by an advisory committee. Investigators from universities, medical centers, the pharmaceutical and allied industries, and the Government, contribute their combined talents to complete projects directed toward specific goals. The Institute's intramural scientists serve as project officers; at the same time, they contribute original research findings to the program. In some instances, they have isolated or identified the organism and developed the original vaccine materials, which were later produced and tested by contract-supported groups.

*Successful oral adenovirus-4 vaccine*

The military has serious problems due to respiratory infections occuring in training camps. When recruits brought from diverse areas live closely together, epidemics of acute upper respiratory infection may break out, resulting in major losses of manpower and money. Much of this illness is caused by the adenoviruses, and by adenovirus type 4 in particular.

Under the respiratory vaccine development program, this Institute developed an oral adenovirus-4 vaccine which produced a symptom-free, noncontagious infection in the intestinal tract, causing the production of antibodies. During the past year this vaccine was used to immunize nearly half a million men in the Army, Navy, and Marine Corps training posts. Hospitalizations were reduced by

more than 60 percent at some bases which had had impending epidemics—the first major payoff for the vaccine development program. The Army has reported that an overall reduction of 44 percent in acute respiratory disease as compared to the previous year's experience was achieved by this large-scale immunization and that pneumonia was reduced to the lowest level seen in its training centers since 1950. Estimates by the Army of money saved by the decrease in lost training days, lowered hospitalization rates, and lowered cost of retraining following hospitalization range as high as $18 million.

*Trivalent parainfluenza vaccine*

Parainfluenza viruses 1, 2, and 3 cause about 20 percent of the acute respiratory diseases serious enough to hospitalize infants and small children. Spreading rapidly from person to person, they cause illness in the form of croup, bronchitis, and pneumonia. These viruses were first isolated in the Institute's intramural laboratories, and separate injectable killed vaccines against each of these three types were among the earliest developed by the respiratory vaccine development program. After safety testing in adult volunteers, trials in small children were found to be 90- to 100-percent effective in stimulating a significant rise in antibody. The three separate vaccines were then combined into a single trivalent one. So far, however, the results with the trivalent vaccine have been disappointing. Little protection against infection has been evident. New techniques of concentrating and improving the viral antigens are being pursued.

*Mycoplasma pneumoniae vaccine*

*Mycoplasma pneumoniae* accounts, in epidemic years, for 10 percent of all respiratory illness in small children, and in the age group from 10 to 20 years causes up to 30 percent of all pneumonia. It has been the object of extensive work in an effort to develop an effective vaccine. Several vaccines have been prepared against *M. pneumoniae* that evoked good antibodies in experimental rabbits and hamsters. Promising results were also seen in small-scale studies in humans. But in large-scale trials, vaccines were only about 50-percent effective in preventing illness.

New vaccines are now being sought which will stimulate the production of adequate protective antibody.

*Respiratory syncytial virus vaccine*

The respiratory syncytial virus is responsible for the death of an estimated 5,000 infants a year—half of the babies who die from acute respiratory diseases. Infants under 6 months are particularly susceptible, although almost no one is immune to the virus. Because of the high mortality rate associated with this disease, it is extremely important that an effective vaccine be developed against it. The organism, however, presents the peculiar problem that even a severe infection does not leave the patient immune. Very small trials have been made with vaccines developed under the vaccine development program, unfortunately with no success. A great deal of further study is needed on this virus. Recent work on the development of a low temperature adapted strain of RS virus in the intramural laboratories may prove an asset in the production of vaccines.

*Preparation and testing of rhinovirus vaccines underway*

The rhinoviruses, of which there may be as many as 100 different types, are primarily responsible for causing the common cold. Although most of these illnesses are quite mild, they run up medical bills, lower productivity, cause absenteeism, and lead to poor performance by students and wage earners. They also lower their victims' resistance to other, more virulent infections. Some experimental vaccines are now being tested, and others in preparation will be tested as they become available.

*Pneumococcal pneumonia vaccine sought*

The vaccine development program is exploring the possibility of developing a vaccine against pneumococcal pneumonia, which may be responsible for as many as 40,000 deaths annually. The highest mortality from this disease is in persons 50 years or over, or chronically ill patients, who often develop an overwhelming infection before antibiotics can be effective. The Institute has awarded a contract for the study of currently prevalent pneumococcal types which cause serious illness, with a goal of developing a polyvalent vaccine incorporating several of these types.

*Promising streptococcal vacine to be promoted*

The intramural laboratories of this Institute conduct a variety of basic studies on streptococci, and studies supported by grants investigate many aspects of the problems involved with this organism. An extremely interesting experimental vaccine material has been developed by one of these grantees. It consists of a highly purified nontoxic, M protein antigenic component of group A streptococcus (the main group causing human disease). It is the M protein antigen that protects the streptococci against being eaten by scavenger cells in the body, so antibodies developed against it would destroy the bacteria's means of defense. In a very small study in children, this material produced antibodies to streptococci without causing undesirable side reactions. Better immunizing preparations are being sought at this time, and if additional currently planned limited trials should prove successful, larger trials will be conducted to determine whether the material will protect against naturally occurring disease. A long-term goal would be the production of a polyvalent vaccine, containing antigens from eight or 10 of the 50 types of group A streptococci which cause the most disease. The Institute will seek to further progress on this interesting vaccine material.

Because of the risk of producing hypersensitivity—thought to be a factor in the development of rheumatic fever and glomerulonephritis—work toward a vaccine must be undertaken with the greatest caution. The question of whether M protein will induce hypersensitivity remains to be investigated thoroughly. Some scientists believe that the protein can be separated, dividing the portion which can produce hypersensitivity from the portion which produces immunity, thus assuring elimination of this possibly undesirable effect.

### A LOOK TO THE FUTURE

Strenuous efforts will be continued to improve the *M. pneumoniae* and the trivalent parainfluenza vaccines, and to perfect a vaccine against the respiratory syncytial virus. Rhinovirus vaccines are being tested as they become available, and new ones are being prepared. Bacterial vaccines will be sought against pneumococci and streptococci. Limited contact support is being given to survey prevalent types of pneumococci and to promote further studies on an interesting streptococcal vaccine material recently developed by an Institute grantee.

## Emphysema and Chronic Bronchitis

Emphysema is a vital public health problem in the United States. Little more than 20 years ago, deaths due to emphysema and chronic bronchitis numbered about 2,300 a year. By 1964, the annual death toll had reached almost 22,000; in 1965, it had soared to nearly 26,000. Mortality from emphysema and chronic bronchitis appears to be doubling about every 5 years. Unless this trend can be reversed, by 1972, deaths from these causes could well reach 64,000.

In 1965, some 18,000 new victims of emphysema and chronic bronchitis were awarded approximately $21 million in social security disability pensions. And a total of some $90 million in disability pensions were paid in 1966 because of these diseases.

In health interview surveys conducted between July 1966 and June 1967, nearly 5 million Americans reported symptoms of bronchitis, emphysema, or a combination of both. The National Disease and Therapeutic Index, based on a sample of visits to the offices of private physicians, indicates that in 1965, among new patients visiting their physicians, approximately 800,000 were diagnosed as having emphysema or chronic bronchitis. Some surveys have yielded estimates that at least 3 percent of all persons over 40 have early signs of chronic obstructive lung disease. Other small surveys suggest that as high as 25 percent of the population over 40 may have some degree of impaired lung function. These surveys, when projected, suggest an estimate of up to 14 million Americans in various stages of chronic obstructive lung disease.

### THE NATURE OF EMPHYSEMA

Emphysema is a chronic, often progressive disorder of the lung in which, the alveoli—tiny air sacs clustered around the ends of the bronchial tubes—are attacked and permanently damaged.

In the normal lung, fresh oxygen is drawn into the blood stream and waste carbon dioxide is removed through the small blood vessels in the walls of the aveoli.

In emphysematous lungs, the walls of the aveoli are irreversibly destroyed and broken down, resulting in large, inefficient air spaces devoid of small blood vessels. The flow of air is resisted, gas exchange impaired, and breathing becomes extremely strenuous. Meanwhile, the heart must pump harder to circulate oxygen-poor blood to body tissues. If the patient is untreated or treated too late, he may suffocate or die of an overworked heart.

### A SEARCH FOR BETTER TREATMENT

To provide hope and relief to those disabled by emphysema, research has been conducted and supported by the Public Health Service—including the National Institutes of Health—in the early detection and treatment of the disease. Pulmonary function tests have been developed. Drugs and inhalation therapy techniques have been tested. Pilot rehabilitation centers have been established to train physicians, nurses, and technicians specializing in the treatment of emphysema patients. Investigators are probing the possible relationship between smoking and air pollution and emphysema.

### BEYOND TREATMENT TO PREVENTION

The medical profession realizes that an all-out effort is necessary to ease the suffering of those now afflicted with emphysema. However, it is also recognized that to reduce the rate of death and disability, intensified efforts must be focused on research into the cause and prevention of the disease.

The cause or causes of emphysema are not now known. At one time, it was considered a disease entity affecting only the aveoli, tiny air sacs clustered around the ends of the bronchial tubes deep in the lung tissue. However, some scientists now suspect that emphysema is actually a cluster of conditions possibly precipitated by a series of "insults" to one or more portion of the respiratory tract. These insults may be acute viral and bacterial infections, allergic reactions such as asthma and hay fever, or the inhalation of noxious agents such as cigarette smoke or the soot and fumes of urban environments. Other investigators believe that substandard living conditions and genetic factors may contribute to chronic obstructive respiratory disease conditions.

### THE SEARCH FOR CAUSES

The 89th Congress, recognizing the need for a program of basic research with a long-term goal of prevention, appropriated an additional $1 million to the National Institute of Allergy and Infectious Diseases, for investigations into the causes of emphysema. In this effort, the strategy of the Institute has been to utilize the interrelated disciplines of allergy, immunology, virology, pathology, microbiology, and cellular biology.

### DEATHS UNDERREPORTED

NIAID grantees at the University of Colorado Medical Center have maintained an emphysema registry for the past 10 years in an effort to obtain data for testing the hypothesis that a number of different acquired disease conditions are involved in emphysema. In monitoring their registry, the scientists have discovered that many deaths actually attributable to emphysema and chronic bronchitis find their way into vital statistics records as deaths due to such associated conditions as pneumonia, heart failure, and sometimes stroke. In their recording of the nature and extent of gross and minute changes in the lungs, the Colorado investigators are now beginning to relate atrophy and thinning of airway walls to a physical flabbiness of the walls, which results in a ready collapse of the bronchial tubes on expiration. Their studies also include the location, nature, and degree of airway obstruction and the effect on total lung capacity.

### CIGARETTE SMOKING AND SOCIOECONOMIC FACTORS

At Harvard University and Boston City Hospital, scientists are describing the mechanism by which cigarette smoking may impair the protective processes of the lung and thus increase its susceptibility to microbial infection.

They are also evaluating the effect of socioeconomic conditions on the progression of chronic progressive respiratory disease. Current indications are that the disease is more severe in lower social and economic groups.

### LUNG DAMAGE AND LUNG REPAIR

Scientists at Duke University School of Medicine in Durham are pursuing the hypothesis that emphysema may represent an attempt by the lungs to repair alveoli damaged by infection, air pollution, allergic reactions, and genetic disorders of connective tissue.

The Duke grantees are using several approaches to explore lung damage and repair at the cellular and subcellular levels. They are attempting to characterize the response of respiratory tract cells when challenged by potentially injurious agents such as airborne contaminants acting in consort with microbial agents. Tho shed light on the process by which inhalated particles are cleared from the lower portions of the human lung, the scientists are studying the clearance mechanism of frog lungs. And they are conducting other investigations—primarily in patients with emphysema and chronic bronchitis—correlating measurements of pressures and flow in the lung with airway structures in an effort to explain why air movement becomes difficult in diseased lungs.

The cilia—tiny hairlike cell projections attached to the lining of the respiratory tract—are being examined meticulously for their role in chronic respiratory diseases. In their healthy state, cilia vibrate and, by their constant motion propel mucous and foreign matter (such as dust and pollen) toward the mouth where it can be removed by "clearing the throat." The Duke University studies indicate that clearance of this foreign matter is enhanced by water deposition, increased temperature, and breathing movement, and is reduced by drying.

### RADIOACTIVE GOLD TRACED

Another team of scientists—working at Hektoen Institute for Medical Research in Chicago—are also studying lung clearance and the effects of microbial agents on the activity of the cilia. Disappearance of particles labeled with radioactive gold is being observed in normal subjects and in patients with chronic bronchitis and emphysema. Results are being correlated with bacteriological, virological, and immunological analyses of bronchial secretions and biopsy specimens.

### PULMONARY EMPHYSEMA OF HORSES SIMULATES DISEASE IN MAN

At Yale University School of Medicine, scientists are assessing the role of viruses, mycoplasmas, and other microbial agents in the causation of emphysema. At a nearby VA hospital patients with emphysema are contributing to a study of blood specimens, waste products and, when possible, bronchial secretions.

Because of the anatomical similarity of the horse's lung to that of man—and because pulmonary emphysema of the horse (commonly known as the heaves) closely simulates emphysema in man—a preliminary investigation of this equine disease has been undertaken. In examining the lungs of horses exposed to urban environment and those living in rural areas, it was found that nearly all of the older horses examined had severe emphysema while the younger animals showed little if any evidence of the disease. Further studies are underway to try to determine whether viruses and other infective agents play any role in the causation of equine emphysema and bronchitis.

### PULMONARY FUNCTION STUDIED

At the University of Utah College of Medicine, 150 patients with chronic bronchitis or emphysema are being studied to determine the relaitonship of age, sex, race, residence, and occupation to the diseases.

The Utah grantees have developed a complete pulmonary function laboratory where patients in early stages of the disease are tested and followed over many years. Of particular interest is the role of infection in the natural history of the disease. Complete studies of lung functions are made periodically to correlate bacteriologic findings with the disease's progress. A technique called transtracheal aspiration makes possible withdrawal of secretions from deep in the lung to more thoroughly explore the events occurring in this vital segment of the organ.

### PRIMARY AND SECONDARY CAUSES

Northwestern University investigators are using the same technique in an attempt to pin-point the principal and secondary factors in the progression of chronic obstructive lung disease. Studies are being conducted with 25 patients and five control subjects who have pneumonia, using transtracheal aspiration to

obtain secretions for bacterial, fungal, mycoplasmal, and viral cultures. A search is also being made for possible autoimmune hypersensitivity factors in the development of chronic lung disorders.

### INFECTION AND IMMUNITY IN CHRONIC BRONCHITIS

Similar microbial organisms found in the nose and throat are being investigated by scientists at the University of Vermont. Particular emphasis is being placed on an assessment of the protective role of immunoglobulin and antibody in respiratory secretions and serum. And the effects of antibiotic therapy and viral vaccines on the course of bronchitis are being evaluated.

### A COMMUNITY UNDER CONTINUAL OBSERVATION

Scientists of the School of Public Health at the University of Michigan for some years have been conducting health and disease investigations in a typical American community at Tecumseh, Mich. In early studies (supported by the National Heart Institute), it was discovered that more than 10 percent of the population over age 15 (or 550 individuals) had chronic cough and sputum production, both common symptoms of chronic bronchitis. Now under NIAID support, persons with established or early chronic pulmonary diseases are followed intensively and their symptoms recorded weekly. If a change develops in an individual's usual state of health, specimens are collected to determine whether viruses or other microbial organisms are present. Working on the hypothesis that healthy relatives of emphysema victims are more likely to develop the condition than the general population, members of the family of patients with chronic pulmonary disease are also being kept under continual medical observation.

### SMOG AND LUNG ARCHITECTURE

At the University of Southern California School of Medicine, scientists are evaluating the relationships between the individual components of smog in the Los Angeles area and the production of chronic bronchitis, emphysema, and certain virus infections.

Studies of mice exposed for several weeks to air containing different concentrations of nitrogen dioxide ($NO_2$) showed marked inflammatory changes in lungs and alteration in lung structure. When the animals were removed from the $No_2$ atmosphere, the inflammation subsided but the lung architecture did not return to normal. The alveoli were enlarged and in some cases had ruptured walls, similar to the changes seen in emphysema of man. The USC grantees also found that animals with lungs damaged by $NO_2$ inhalation were more susceptible to airborne bacterial infections. Studies are continuing to determine what alterations in the lungs may be brought about by $NO_2$ and such virus infections as influenza.

### RESPIRATORY TRACT ANTIGENS DISCOVERED

Scientists at Baylor University College of Medicine in Houston are seeking additional knowledge regarding the basic immunologic characteristics of the cells which line the respiratory tree. Their experiments led to the discovery of antigens (antibody-producing substance) which are unique to the respiratory tract. These antigens also have been found in the sputum of patients with various respiratory diseases. Current investigations involve the purification of these antigens and further study of antigens in the sputum of patients.

### A STUDY OF THREE RACES

Investigators at the University of Oklahoma Medical School are attempting to determine whether emphysema prevalence differs in three racial groups: Caucasian, Negro, and American Indian. This study is based in part on earlier reports that a deficiency of antitrypsin (a substance which inhibits the action of the pancreatic enzyme trypsin) is a genetic characteristic and is related to chronic obstructive lung disease. Also, the Oklahoma scientists are evaluating the presence of various organisms in the sputum in the development of obstructive lung disease.

### INFECTIOUS AGENTS AND PULMONARY FUNCTION

NIAID grantees at Washington University School of Medicine in St. Louis have undertaken a systematic evaluation of the effects of acute virus and cycoplasma respiratory infections on the pulmonary function of adults. Their hypothesis is that such infections cause temporary abnormalities in pulmonary function which persist beyond the acute illness and perhaps lead to chronic disease. Thus, what otherwise would be minor infections may prove serious in cases of chronic pulmonary disease because of the added burden of diminished pulmonary function. These studies are being conducted with 50 medical and nursing students and with 50 patients with chronic pulmonary insufficiency, using appropriate techniques for isolating viruses, mycoplasmae, and bacteria from throat swabs and stool specimens at regular intervals and during periods of acute respiratory infections.

### TEARS AND EXHAUST FUMES

At the Research Foundation of State University of New York in Albany, two studies are currently underway on lysozyme (a protein found in saliva, tears and many animal fluids) which acts as a bacterial enzyme.

In one investigation, the scientists are collecting tears from patients with chronic bronchopulmonary disease, for quantitative analysis of immunoglobulin content of lysozyme activity. Such information may lead to earlier diagnosis of these conditions.

The second study—a new approach to the subject of air pollution and tissue damage—involves the immunologic reactivity of certain nitro-olefins, thought to be important constituents of automobile exhaust fumes. The primary goal of this project is to observe the effect of inhalation of notro-olefins in sensitizing guinea pigs and in producing lung disease.

### OTHER STUDIES CONTINUE

In addition to the emphysema research activities described above, the Institute also supports the following parallel investigations which may provide valuable leads to the knowledge of emphysema and other chronic obstructive disorders:

A study at the University of Illinois on the relationship of repeated infections and the progression of chronic bronchitis.

An appraisal by scientists at Louisiana State University on the impact of combined viral and bacterial infections on respiratory function.

An evaluation by University of Pennsylvania scientists of the relationships between bronchiolitis (a disease in which the small bronchioles are destroyed) and allergic asthma.

One of the major problems confronting scientists seeking the cause of emphysema is the need for a laboratory animal model. Such an animal, living in a controlled environment, could be subjected to the same factors suspected of precipitating the disease in humans and the efficacy of various regimens for treatment and prevention could be evaluated. Steps toward this goal were taken in 1967 when the first interdisciplinary symposium on the subject was jointly sponsored by the Institute and the Division of Research Grants. Seventy scientists and physicians shared their knowledge and views as to natural and experimental animal models for the study of emphysema. Animals considered to warrant more intensive investigations were the germ-free rat, the horse, and the pig.

### INTRAMURAL RESEARCH

Scientists at the Institute's Maryland and Montana laboratories continue to make contributions to the search for knowledge about the role of viruses and other micro-organisms in chronic degenerative diseases. Recent reports from the NIAID laboratories revealed that when viruses attack the hair-like cilia projecting from the lining of the respiratory tract, the cilia lose their normal ability to propel foreign matter out of the tract. This inability, it has been suggested, may be one of the early steps leading to chronic obstructive respiratory disease.

A LOOK TO THE FUTURE

Since there are no clear-cut leads as to the cause or causes of emphysema, no quick solution to the problem can be anticipated. Many complex questions remain to be answered. This Institute believes that these answers will emerge from the multidisciplined approach being pursued. Prevention of emphysema will require the efforts and support of scientists, medical educators, public health officials, Government leaders, and the American people.

GORGAS MEMORIAL LABORATORY

Mr. FLOOD. Regarding the Gorgas Memorial Laboratory, they receive $500,000 in grants a year. Are we getting our money's worth out of that?

Dr. DAVIS. I think we are getting our money's worth. They are doing very excellent research on infectious diseases in an area of Central America which is of major concern to the United States. They have a strong staff which is increasing in capability. They feel there are many problems which are not dealt with here completely in the United States.

One of their studies, for instance, concerns malaria in South American monkeys which might be transmitted to man or which can be used for evaluation of drugs. They are interested in the insect-borne viruses of that part of the world which could invade the United States. They have a good study in diarrheal diseases of children.

Mr. FLOOD. Do you get regular reports from these people?

Dr. DAVIS. Yes, sir.

Mr. FLOOD. Do your people audit this institute?

Dr. DAVIS. We receive regular reports.

Mr. FLOOD. Do you audit this institution?

Dr. DAVIS. The $500,000 is audited——

Mr. MAGRUDER. I do not think we do, sir. This is handled, I believe, by a board of directors, of which there is a treasurer. I cannot remember his name. Mr. Simpson is the secretary of the board of directors.

Mr. FLOOD. You mean they audit themselves?

Mr. MAGRUDER. No; they have an audit but I do not think it is a responsibility of our agency. We just handle the transfer of the funds.

Mr. FLOOD. Should it be?

Dr. SHANNON. Mr. Chairman, this is a responsibility of the Department which has the general audit function for all of these programs. This is the fiscal audit.

Mr. FLOOD. That is right.

Dr. SHANNON. The scientific audit, if you will, takes place via visits and by their annual report.

Mr. FLOOD. I meant fiscal.

(The following was subsequently submitted:)

The General Accounting Office performs annual examinations of the financial statements of the Gorgas Memorial Institute. By an arrangement between the Comptroller General and the President of the Gorgas Memorial Institute, the report of the annual audit of the records of the Institute is included in the annual report of the work and operations of the Gorgas Memorial Laboratory for the same fiscal year. This report is transmitted annually to the Congress by the President of the Gorgas Memorial Institute.

Dr. DAVIS. I have here a copy of the 39th annual report.

Mr. FLOOD. What year?

Mr. DAVIS. This is dated January 23, 1968.

SUMMARY OF 1969 BUDGET REQUEST

Mr. FLOOD. You gave us what your budget is for 1968, $93,502,000, and your request for 1969 is $98,562,000. That is an increase of $5,060,000. Two-thirds of this is going for research grants, which will allow you to support about 100 more research projects. This is a pretty fair budget compared to the budgets submitted by the other witnesses who have occupied that chair you are sitting in.

You are budgeting for a slight decrease in the number of fellowships, and the number of training grant programs. Why do you place the emphasis on research over training? Yours seems to be about the only institute that does that.

Dr. DAVIS. In view of all of the requirements of the Institute, we have come to the conclusion that this is about the right proportion of funds to go into training grants and fellowships in regard to the research projects which can be supported. Actually, even though there is a slight increase in funds, we have a decrease in the number of fellowships and training grants which we can support next year.

Mr. FLOOD. I mentioned there is a decrease in the number of fellowships and training grants. Are you emphasizing research over training?

Dr. DAVIS. We try to keep a balance, Mr. Flood.

Mr. FLOOD. But you did not.

RESEARCH GRANTS

Dr. DAVIS. Actually, the increased number of grants which we will be able to support next year is all accounted for by commitments made to grants either this year or in previous years.

For instance, we do not have money to increase our new competing grants at all. We can fund 394 competing projects in 1968 and we are budgeting the same number of new competing projects in 1969.

Mr. FLOOD. On this subject of research grants, suppose you take a look at page 214 of your justification, and I quote:

> The Institute has developed a structured procedure for determining and funding grants in areas of special emphasis.

The language never ceases to astound me. What is that procedure? How in the world is that any different from what we thought you have been doing? Does it differ from the way the other Institutes operate? Does it change the role of the Advisory Council in any way with your Institute as against the others? If it does, how does it do it?

Dr. DAVIS. I think we are doing essentially the same as the other Institutes; namely, identifying certain areas within our mission which are either neglected or of such overriding importance we feel they need particular attention.

For instance, we have identified the special emphasis areas, such as drug resistance, antiviral substances, infectious hepatitis, chronic and degenerative diseases, streptococcal infections, emphysema, and chronic lung disease, transplantation immunology, clinical allergy, and immunology.

We have developed information which indicates that these should be supported perhaps at the expense of some of the other wider ranging areas.

Mr. FLOOD. Does this change the role of the Advisory Council?

Dr. DAVIS. Yes. We reported this analysis to the Advisory Council at our meeting last June. After considerable discussion, the Council agreed with us in general that these were the areas that needed to have particular concern, and from time to time we identify grant applications which fall within these areas and which we feel should certainly be paid, even if we may have to drop out some of the others.

### COLLABORATIVE RESEARCH

In our collaborative program, we have identified four areas for collaborative development and funding by contracts. These are vaccine development, rubella vaccine, transplantation immunology, and a group we call reference reagents. In collaborative areas where contract funding is used, the staff takes a much more active part in encouraging and directing work and also in the communications network of the people who are engaged in these particular studies. In this way we can have a much better focus and can move ahead much faster.

Our tissue-typing program I think is a good example of collaborative research where, as I mentioned, some 3 years ago we embarked upon an effort to collect special sera useful in tissue-typing, and to distribute these sera to medical centers where transplantations were going on, first, to evaluate them and then, if they were found useful, to actually use them in the selection and management of cases.

And we are glad to say this has worked out very well and I think I can state quite positively that we have accelerated the work of tissue typing by several years simply by a concerted effort on the part of the Institute to do this in a structured way.

### EMPHYSEMA

Mr. FLOOD. We have talked here for a few weeks quite a good deal about emphysema. In view of the fact we mentioned it in the report last year with particular reference to your Institute, do you want to add a little more detail now about what you are doing in the area?

Dr. DAVIS. Mr. Flood, we feel we can make our best contribution in the whole study of emphysema by examining the role of viruses, bacteria, and immunologic processes in the causation and in the development of the disease. So we are now funding about 11 or 12 grants which were encouraged by the Institute along these lines.

These also particularly emphasize the prospective examination of the disease; namely, that we feel we must take a person in the early stages of disease, or even before that, and follow the course of the disease in detail over the long term.

We are doing this in two places, one in California and one in Michigan; we are also identifying the kinds of infections that these patients with emphysema and chronic bronchitis have had.

We have established a registry at the University of Colorado. There are some studies in Oklahoma on emphysema in three different races. Most important of all, perhaps, is the attempt to get an animal model for the disease. As you know, horses have a similar disease known as heaves, and we have a grant support for a study of this disease in horses, with the idea that this might give us a lead on what is really a very, very perplexing problem.

VACCINES AGAINST RESPIRATORY DISEASES

Mr. FLOOD. You told us something about your work on vaccines for the purpose of attacking German measles. What about any other vaccines, especially those for respiratory conditions?

Dr. DAVIS. We have been primarily focusing on vaccines against respiratory diseases of infants and children. And this has gone along very well in some cases, but it is turning out to be a very difficult problem in others. We have several vaccines which have been produced and are being evaluated. One, for a group of parainfluenza viruses, is being evaluated in a small number of children. This virus group causes the ordinary bronchiolitis or croup in children.

WHOOPING COUGH

Mr. FLOOD. What is whooping cough?

Dr. DAVIS. Whooping cough is a specific disease caused by particular bacteria known as pertussis bacteria. These are not viruses but bacteria. Fortunately, this disease is very well under control with the aid of a vaccine which is widely used.

TUBERCULOSIS

Mr. FLOOD. The committee has been listening to you for about 10 years on this business of a TB vaccine. I got the impression over recent years that you were pretty optimistic about this. What has happened to it?

Dr. DAVIS. I would say we have probably reached a plateau in the last year or two. The lines along which we have been working is to fractionate the tubercle bacillus so as to obtain the most active immunizing fraction which will not sensitize individuals. Our work in mice as of several years ago was very encouraging.

When we extended this to monkeys, and on a broader scale, we found that there were still very great problems. But we believe that the concept is right, that one should eventually get an immunizing fraction from the TB bacillus which does not cause the sensitizing phenomenon. If and when we do that, we should have a much better vaccine.

CANCER

Mr. FLOOD. What about a vaccine for cancer, if you are not busy?

Dr. DAVIS. This will take a long time and a great deal of work.

Mr. FLOOD. Have you a program directed toward this end in your institute?

Dr. SHANNON. I will tell you what has happened there. Dr. Davis is hesitating.

The Cancer Institute is trying to steal his best virologist to bring the problem back over to the Cancer Institute.

Dr. DAVIS. We still have a lot of good virologists.

Dr. SHANNON. He is planning to leave the Allergy Institute to pull together activities that relate to the viral origin of cancer.

DRUG RESISTANCE BY BACTERIA AND VIRUSES

Mr. FLOOD. Here is something that always interests me. Just about the time you turn out a new drug to cure some of these infections, the bugs begin to enjoy it and eat it for dessert. Why is that?

Dr. DAVIS. This is true in some forms of drug therapy, against bacteria particularly.

Mr. FLOOD. How do they do that?

Dr. DAVIS. I will tell you what they do: Some actually have what we call an "R" factor, a resistance factor, which bacteria can transmit to their progeny, or in some cases to related bacteria. And this factor is the reason why large numbers of bacteria suddenly become resistant against the drug. They have singled this out by some form of evolution and thereby protected themselves. But this work has just been developed within the last couple of years.

ALLERGIES

Mr. FLOOD. What about vaccines for allergies generally? What is the progress in that area?

Dr. DAVIS. I wish we could report more rapid progress, but the proggress, although it is not rapid, is steady.

Allergies affect about 20 million people in the country. Hay fever is one of the most important.

Mr. FLOOD. What about that? My, that is widespread, is it not?

Dr. DAVIS. Yes. It covers the whole United States except the northwest portion.

Mr. FLOOD. What do you think? What about the light at the end of the tunnel?

Dr. DAVIS. We are attempting to fractionate and break out part of the protein chemical substance in the pollen grain which produces the sensitivity, and actually, there have been two fractions, named "fraction E" and "fraction K," which do have specific action. And these are now being evaluated in some of the allergy clinics, both from the standpoint of their diagnostic usefulness in specifying which of the various causes of hay fever it may be, and also in desensitizing these individuals so they will not react so strongly. This is the kind and direction of the work which is being done.

The other direction of work, of course, is the pharmacological approach, namely, neutralizing the histamine and histamine-like substances. But we have had antihistamines for many years now and there have not been any new developments along this line; although it is an area which is very important and we have tried to encourage people to get into the area, and I hope we can do more in the future.

BACTERIA RESISTANCE TO DRUGS

Mr. FLOOD. After these bacteria develop a resistance, what do you do then? I am a physician and I call you up and report that this drug isn't effective on my patient. And you get a lot of calls in the next 4 or 5 months from all over the country and they all tell you the same thing. What do you do?

Dr. DAVIS. At the present time, the best approach we can take is to

try to understand better what the factors are, to try to develop more classes of drugs which might be unfamiliar to these organisms.

Mr. FLOOD. Do you have a specific example of one?

Dr. DAVIS. One organism, meningococcus, is one which becomes quite resistant to sulfa drugs. And in fact, as you are aware, it has been a problem to the military because many of the men recruits coming into military training apparently carry a large number.

Mr. FLOOD. It flares up periodically?

Dr. DAVIS. It does.

Actually, there was an outbreak in a hospital in Warren, Pa., in which the young resident physician died and there were several other cases there. It is a very dangerous and dramatic disease. The disease can be controlled by penicillin usually if the drug therapy is administered in time, but it is a very rapidly progressing disease.

HEPATITIS

Mr. FLOOD. I like shellfish, clams, and oysters and drink a lot of water and like fish. Should I be afraid of hepatitis?

Dr. DAVIS. Hepatitis is a major disease in this country and it is even worse in other countries. As you indicate, it is associated with food. The agent which causes the disease has not yet been identified, it is presumably a virus because it does act like a virus. There has been some promising work in Chicago by a scientist who thinks they can infect a small monkey, the Marmoset. This work has also been done here in our own laboratories and in Dr. Melnick's laboratory in Houston.

The work is unconfirmed at the present time by the very extensive studies. All I can say is we are hopeful.

Mr. FLOOD. This has reached epidemic proportions?

Dr. DAVIS. Yes.

Mr. FLOOD. How is it contagious?

Dr. DAVIS. In two ways. One is, as you indicated, actual ingestion of contaminated food or water, and then we know that it probably can be transmitted from one person to another, particularly between children.

Mr. FLOOD. It is infectious as well?

Dr. DAVIS. Yes. It is quite infectious in infants and children.

CHOLERA

Mr. FLOOD. There has been interest in the press, because of our involvement in Southeast Asia, in the recurrence of cholera in certain areas of Asia. The United States has people coming back, military and civilians as you know. What is your organization doing to stay on top of the problem?

Dr. DAVIS. As you are aware, the SEATO organization is sponsoring an extensive study on cholera in Southeast Asia and we are cooperating in this country with funds, a large part of which actually come from the AID, but the scientific direction for the study on cholera is primarily in NIH and in our Institute. Dr. Seal, who is behind me, is the Chairman of the NIH Cholera Research Laboratory.

Mr. FLOOD. What causes cholera?

Dr. DAVIS. It is caused by a bacterium, vibrio comma, which is endemic in certain areas, it is widespread in water, food, and transmitted primarily by water and by food.

Mr. FLOOD. Do we have any in the United States?

Dr. DAVIS. No, we have not.

Mr. FLOOD. Never had any?

Dr. DAVIS. Never had any since—well, many years, 1908, something like that. There were many epidemics of cholera in the last century.

Mr. FLOOD. In continental United States?

Dr. DAVIS. Yes.

Mr. FLOOD. Mr. Casey?

Mr. CASEY. I have no questions, Mr. Chairman.

Mr. FLOOD. Thank you.

JUSTIFICATION MATERIAL

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $94,422,000 | $98,562,000 |
| Proposed transfer to "Indian health activities" | -224,000 | 0 |
| Total | 94,198,000 | 98,562,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 214 | Research | | $52,264,000 | | $55,627,000 | | +$3,363,000 |
| | General research support grants | | (5,169,000) | | (5,289,000) | | (+120,000) |
| | Gorgas Memorial Laboratory | | (500,000) | | (500,000) | | (0) |
| | Categorical clinical research centers | | (1,100,000) | | (1,100,000) | | (0) |
| | Scientific evaluation | | (50,000) | | (50,000) | | (0) |
| 218 | Fellowships | | 4,267,000 | | 4,362,000 | | +95,000 |
| 219 | Training | | 9,251,000 | | 9,488,000 | | +237,000 |
| | Direct operations: | | | | | | |
| 221 | Laboratory and clinical research | 628 | 14,852,000 | 642 | 15,142,000 | +14 | +290,000 |
| 226 | Collaborative research and development | 33 | 11,023,000 | 33 | 12,034,000 | 0 | +1,011,000 |
| 231 | Review and approval of grants | 55 | 1,479,000 | 57 | 1,504,000 | +2 | +25,000 |
| 232 | Program direction | 25 | 366,000 | 27 | 405,000 | +2 | +39,000 |
| | Total obligations | 741 | 93,502,000 | 759 | 98,562,000 | +18 | +5,060,000 |
| | Unobligated balance, reserve | 23 | 696,000 | 0 | 0 | -23 | -696,000 |
| | Total, obligations and reserve | 764 | 94,198,000 | 759 | 98,562,000 | -5 | +4,364,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions.... | 741 | 759 | +18 |
| Full-time equivalent of other positions | 6 | 6 | 0 |
| Average number of all employees..... | 691 | 705 | +14 |
| 11 Personnel compensation: | | | |
| Permanent positions..... | 6,136,000 | 6,371,000 | +235,000 |
| Positions other than permanent... | 53,000 | 53,000 | 0 |
| Other personnel compensation..... | 147,000 | 149,000 | +2,000 |
| Total personnel compensation... | 6,336,000 | 6,573,000 | +237,000 |
| 12 Personnel benefits..... | 780,000 | 798,000 | +18,000 |
| 21 Travel and transportation of persons | 300,000 | 300,000 | 0 |
| 22 Transportation of things..... | 75,000 | 75,000 | 0 |
| 23 Rent, communications, and utilities | 230,000 | 230,000 | 0 |
| 24 Printing and reproduction..... | 45,000 | 45,000 | 0 |
| 25 Other services..... | 1,046,000 | 1,101,000 | +55,000 |
| Project contracts..... | 10,641,000 | 11,800,000 | +1,159,000 |
| Payment to "National Institutes of Health management fund"..... | 5,428,000 | 5,331,000 | -97,000 |
| 26 Supplies and materials..... | 2,207,000 | 2,200,000 | -7,000 |
| 31 Equipment..... | 650,000 | 650,000 | 0 |
| 41 Grants, subsidies and contributions | 65,782,000 | 69,477,000 | +3,695,000 |
| Subtotal..... | 93,520,000 | 98,580,000 | +5,060,000 |
| Deduct quarters and subsistance charges | -18,000 | -18,000 | 0 |
| Total obligations by object... | 93,502,000 | 98,562,000 | +5,060,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $94,422,000 |
| Proposed transfer to "Indian health activities" | -224,000 |
| Unobligated balance, reserve | -696,000 |
| 1968 total estimated obligations | 93,502,000 |
| 1969 estimated obligations | 98,562,000 |
| Total change | +5,060,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of pay costs | --- | --- | --- | $81,000 |
| 2. One additional day of pay in 1969 | --- | --- | --- | 19,000 |
| B. Program | | | | |
| 1. Research grants | --- | $52,264,000 | --- | 3,363,000 |
| 2. Fellowships | --- | 4,267,000 | --- | 95,000 |
| 3. Training | --- | 9,251,000 | --- | 237,000 |
| 4. Laboratory and clinical research | 628 | 10,379,000 | 14 | 325,000 |
| 5. Collaborative research and development | 33 | 10,972,000 | --- | 1,000,000 |
| 6. Review and approval of grants | 55 | 695,000 | 2 | 17,000 |
| 7. Program direction | 25 | 246,000 | 2 | 20,000 |
| Total program increases | --- | --- | 18 | 5,057,000 |
| C. Payments to the "National Institutes of Health management fund" for centrally furnished services | | | | |
| Laboratory and clinical research | --- | 4,473,000 | --- | -$118,000 |

| | Base | | Changes from Base | |
|---|---|---|---|---|
| | Positions | Amount | Positions | Amount |
| Collaborative research and development..... | --- | $51,000 | --- | $4,000 |
| Program direction..... | --- | 120,000 | --- | 17,000 |
| Total management fund | --- | --- | --- | -97,000 |
| Total net changes requested..... | --- | --- | +18 | +5,060,000 |

Explanation of Changes

Research grants--The $3,363,000 increase will provide $3,243,000 for approximately 101 additional project grants and $120,000 for general research support grants.

Fellowships--The increase of $95,000 will support continuation of the fellowship program and provide "cost-of-living" increases inherent in the program.

Training grants--The increase of $237,000 will support continuation of the graduate training program and provide for the annual incremental increase experienced yearly in this activity.

Laboratory and clinical research--The increase of $325,000 and 14 positions will provide for studies in the clinical allergy and immunology, and viral mycoplasma and rickettsial diseases.

Collaborative research and development--The increase of $1,000,000 will intensify the Transplantation Immunology Program.

Review and approval of grants--The increase of $17,000 will provide two additional positions to support grants management activities.

Program direction--The increase of $20,000 will provide two additional staff positions.

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act<br>Section 301--Research and Investigation, in general . . . . . | Indefinite |
| Title IV, Part D--National Institute of Allergy and Infectious Diseases. . . . . | Indefinite |

PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justification under the tab, "Preamble Paragraph" in Volume V.

The Public Health Service Act, Title IV, Research Institutes, Part D, National Institute on Arthritis, Rheumatism, and Metabolic Diseases, National Institute on Neurological Diseases and Blindness, and other Institutes.--

"Sec. 431 (b) The Surgeon General is authorized with the approval of the Secretary to establish in the Public Health Service one or more additional institutes to conduct and support scientific research and professional training relating to the cause, prevention, and methods of diagnosis and treatment of other particular diseases or groups of diseases (including poliomyelitis and leprosy) whenever the Surgeon General determines that such action is necessary to effectuate fully the purposes of section 301 with respect to such disease or diseases."

"Sec. 433 (a) Where an institute has been established under this part, the Surgeon General shall carry out the purposes of Section 301 with respect to the conduct and support of research relating to the disease or diseases to which the activities of the institute are directed, through such institute and in cooperation with the national advisory council established or expanded by reason of the establishment of such institute. In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions. The provisions of the subsection shall also be applicable to any institute established by any other provision of this Act to the extent that such institute does not already have the authority conferred by this subsection."

Explanation of Transfers

| | 1968 Estimate | 1969 Estimate | Purpose |
|---|---|---|---|
| Proposed transfer to: | | | |
| "Indian health activities".... | $224,000 | 0 | To cover pay raise costs. |

Justification

National Institute of Allergy and Infectious Diseases

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 741 | $7,116,000 | 759 | $7,371,000 | +18 | +$255,000 |
| Other expenses..... | | 86,386,000 | | 91,191,000 | | 4,805,000 |
| Total..... | 741 | 93,502,000 | 759 | 98,562,000 | +18 | +5,060,000 |

General Statement

The Institute conducts and supports research on the causes, characteristics, prevention, control, and treatment of diseases believed to be caused by infectious agents including bacteria, fungi, viruses, and parasites--or by abnormalities in the body's immune mechanisms such as allergies. In its attack on infectious and allergic diseases, the Institute is focusing attention primarily on important problems that demand increased research efforts. Two types of programs--nationally organized research programs and special emphasis research programs--have been set up to deal with these problems.

The nationally organized research programs are collaborative, contract-financed, Institute-coordinated efforts carried on by many laboratories to attain a common goal. They are conducted in partnership with industry, university research centers, and other Institutes of NIH. The special emphasis research programs are designed to intensify investigations of critical disease problems in urgent need of increased effort. Special emphasis research programs are also aimed at promoting the exchange of information to help identify and evaluate avenues of research that should be followed. The Institute also supports a large body of free-ranging investigator-inspired research.

The National Institute of Allergy and Infectious Diseases is requesting a total of $98,562,000 for 1969, an increase of $5,060,000 over 1968. This increase is to be directed toward research of allergic and infectious diseases in the following areas: (1) $3,695,000 for support of extramural activities; (2) $354,000 for intramural research and (3) $1,011,000 for the contract program.

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Regular programs..... | $45,445,000 | $48,688,000 | +$3,243,000 |
| Special programs..... | 6,819,000 | 6,939,000 | +120,000 |
| Total research grants..... | 52,264,000 | 55,627,000 | +3,363,000 |

Introduction

The Institute has developed a structured procedure for determining and funding grants in areas of special emphasis. The criteria for selection of the areas were set by staff members of the Institute after lengthy review and were based primarily on morbidity-mortality statistics as a measure of impact upon public health. Staff, in their deliberations, also considered such data as the state of scientific and technical knowledge, resource availability and the current intellectual commitments of the scientific community. The selected programs have been presented to the National Advisory Council for criticism and advice. Staff, along with its advisory groups, continually redefines, redevelops, and reviews these areas.

These procedures resulted in a structured specific mechanism by which the National Advisory Council could review grant applications, not only in terms of scientific merit, but also in terms of their relevance to the public health. The staff with the collaboration of Council is assuring effective attention to research needs of high national import by a system which channels funds into specific areas of research.

In 1968, the National Institute of Allergy and Infectious Diseases plans on supporting approximately 1,384 regular research projects in the amount of $45,445,000. The majority of these projects are ongoing noncompeting continuation grants which were approved for payment by advisory groups in 1967 and prior years for project periods of two to five years. The noncompeting continuation grants represent approximately 70% of this Institute's total regular research program.

Program plans in 1968 and 1969

Allergy and other Immunologic Disorders:

Transplantation Immunology--A base for the future development of a comprehensive approach to the support of research in immunology as associated with organ transplantation has been established by this Institute. Through the influence of the intensified programming activities of staff and through the continued operations of a subcommittee of expert consultants, it is anticipated that the accelerated growth rate of meritorious research grant applications reviewed and recommended for payment by the National Advisory Allergy and Infectious Diseases Council will continue. Renewed emphasis will be placed on the support of basic immunological investigations, because the solution to one of the two principal barriers to practical and successful organ transplantation - rejection of the transplanted organ - lies in the immunological field. The Institute plans to provide $2,839,000 in 1969 for this program.

Bacterial and Mycotic Diseases:

Drug Resistance--The widespread use of potent antimicrobial agents has resulted in a new responsibility of major proportion to public health. More and more strains of bacteria are becoming resistant to a greater variety of drugs. The present arsenal of antimicrobial agents will not continue to be adequate even though their judicious use will minimize the development of resistance to some of the antibiotics developed recently. This phenomenon of drug resistance has been dramatically emphasized by the exhibitions of severe outbreaks of meningococcal infection, staphylococcal disease, and the continuing presence of chronic bacterial disease as demonstrated by chronic pyelonephritis and chronic pulmonary disease. The Institute plans to maintain support for research in this area at approximately $5,283,000 in 1969.

Parasitic Diseases:

Malaria--Despite the immense research effort which has been directed at malaria by work supported by this Institute and particularly by other agencies, several questions remain unresolved. The appearance in recent years of drug resistant strains of human malaria is a serious obstacle to effective treatment. Development and evaluation of new drugs and drug regimens, studies on the biochemical mechanism involved in drug resistant and development of new methods of mosquito control can be expected to provide useful solutions to the problem. The Institute plans to award approximately $598,000 for work in this research area during 1969.

Viral and Rickettsial Diseases:

Chronic and Degenerative Diseases--The Institute has projected a $1,957,000 program in the field of chronic and degenerative diseases of probably microbial origin during 1968. This area includes such dread diseases as emphysema, multiple sclerosis and amyotrophic lateral sclerosis, it also includes chronic kidney diseases (e. g. chronic nephritides of viral and bacterial origin) and vascular disease (e. g. viral and bacterial damage to heart and blood vessels). The possible infectious and immunologic genesis of these diseases is a research area which, until now, has received little attention from the scientific community. There is a significant body of information available which suggests that participation in a broad-fronted attack will be fruitful. The Institute plans to award approximately $2,093,000 in the field of chronic and degenerative diseases in 1969, an increase of $136,000 over 1968. There has been an alarming increase in chronic-progressive respiratory diseases, often resulting in pulmonary emphysema. Additional support in recent years for emphysema studies has permitted a systematic exploration of the role of microbial agents and allergic materials through comprehensive studies in large medical centers where the various interrelating components can be intensively investigated and evaluated.

Infectious Hepatitis--The importance of research on this disease is evidenced by the 1965 statistics of 707 deaths with 34,365 cases reported. These figures do not adequately describe the distress caused by the long recovery period necessary and possibly permanent debilitating effects of this disease. Research in this area has been plagued by two major problems: first there is the problem of finding a convenient reliable laboratory method of isolating and growing etiological

agents; while, on the other hand, there is the equally great problem of establishing by immunologic methods or by host reaction, the significance of those agents which have been isolated. This disease is considered to be of such significance that the Institute has identified it as a special emphasis program. It is planned that staff will strive to identify a resource base which will allow meaningful scientific investment into the problem.

Antiviral Substance--Viral diseases as a single category constitute the largest single cause of morbidity in the United States. In addition, present evidence suggests that many dread diseases of unknown etiology may eventually be shown to be of viral origin.

The great diversity of virus types necessitates the consideration of alternate approaches in combating viral diseases. Despite discovery of a few drugs with activity against specific viruses, no generally useful drugs have appeared for the treatment of viral infections.

Drug therapy in viral diseases must await the development of a rational approach to the synthesis of chemotherapeutic agents. This approach can best be fostered by fundamental studies of the virus-cell interaction and through basic studies of the way in which viruses grow and replicate. Equipped with this basic virological knowledge, investigators may then devise means of disrupting the virus growth for therapeutic purposes.

In recent years, the increasing knowledge of molecular biology including the structure and metabolism of nucleic acid and protein synthesis has produced a large resource base of interest in addition to opening up the possibility of rationally designed antiviral substances. In this area this Institute will support projects amounting to $5,283,000 in 1969.

Special Programs:

The increase of $120,000 requested for general research support grants represents the Institute's proportionate share of the proposed National Institutes of Health increase in this area.

## Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting projects | 990 | $31,844,000 | 1,091 | $35,087,000 | +101 | +$3,243,000 |
| 2. Competing projects | 394 | 13,101,000 | 394 | 13,101,000 | 0 | 0 |
| 3. Supplementals | (60) | 500,000 | (60) | 500,000 | 0 | 0 |
| 4. Subtotal regular program | 1,384 | 45,445,000 | 1,485 | 48,688,000 | +101 | +3,243,000 |
| 5. General research support | | 5,169,000 | | 5,289,000 | | +120,000 |
| 6. Scientific evaluation | (1) | 50,000 | (1) | 50,000 | | 0 |
| 7. Gorgas Memorial Laboratory | | 500,000 | | 500,000 | | 0 |
| 8. Categorical clinical research centers | 5 | 1,100,000 | 5 | 1,100,000 | 0 | 0 |
| 9. Total research grants | 1,389 | 52,264,000 | 1,490 | 55,627,000 | +101 | +3,363,000 |

## Research Grants Program Analysis

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Fields | | | |
| Allergy and other Immunologic Disorders | $9,384,000 | $10,114,000 | +$730,000 |
| Transplantation immunology* | (2,615,000) | (2,839,000) | (+224,000) |
| Bacterial and Mycotic Diseases | 15,217,000 | 16,277,000 | +1,060,000 |
| Drug resistance | (4,939,000) | (5,283,000) | (+344,000) |
| Parasitic Diseases | 5,358,000 | 5,731,000 | +373,000 |
| Malaria | (559,000) | (598,000) | (+39,000) |
| Viral and Rickettsial Diseases | 15,486,000 | 16,566,000 | +1,080,000 |
| Chronic and degenerative diseases | (1,952,000) | (2,093,000) | (+136,000) |
| Antiviral substance | (4,939,000) | (5,283,000) | (+344,000) |
| Subtotal regular program | 45,445,000 | 48,688,000 | +3,243,000 |
| General research support grants | 5,169,000 | 5,289,000 | +120,000 |
| Scientific evaluation | 50,000 | 50,000 | 0 |
| Gorgas Memorial Laboratory | 500,000 | 500,000 | 0 |
| Categorical clinical research centers | 1,100,000 | 1,100,000 | 0 |
| Total research grants | 52,264,000 | 55,627,000 | +3,363,000 |

*Excludes $600,000 in Categorical clinical research centers for 1968 and 1969.

Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total fellowships..... | $4,267,000 | $4,362,000 | +$95,000 |

Program plans in 1968 and 1969

The Fellowships Program is designed to function as an integral part of the research grants and training grants activities. It is intended to increase the availability of trained professional researchers who are preparing to launch their career or who are in mid-career in selected research areas within the categorical interests of the Institute.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting.. | 168 | $3,039,000 | 146 | $2,813,000 | -22 | -$226,000 |
| b. Competing..... | 44 | 608,000 | 44 | 692,000 | 0 | +84,000 |
| 2. Supplementals..... | (7) | 9,000 | (7) | 9,000 | 0 | 0 |
| 3. New..... | 65 | 611,000 | 83 | 848,000 | +18 | +237,000 |
| 4. Total fellowships. | 277 | 4,267,000 | 273 | 4,362,000 | -4 | +95,000 |

Fellowships (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Postdoctoral..... | 110 | $825,000 | 110 | $880,000 | 0 | +$55,000 |
| 2. Special..... | 35 | 396,000 | 35 | 420,000 | 0 | +24,000 |
| 3. Research Career: | | | | | | |
| a. Career..... | 26 | 820,000 | 25 | 710,000 | -1 | -110,000 |
| b. Development awards..... | 106 | 2,226,000 | 103 | 2,352,000 | -3 | +126,000 |
| 4. Total fellowships. | 277 | 4,267,000 | 273 | 4,362,000 | -4 | +95,000 |

Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants..... | $9,251,000 | $9,488,000 | +$237,000 |

Program plans in 1968 and 1969

The Training Grants Program of this Institute provides opportunities for young scientists to receive the background, training and experience which are essential for meeting future manpower requirements within the categorical responsibilities of the Allergy and Infectious Diseases Institute. Newly trained personnel are especially essential to insure continued progress in such rapidly expanding areas as virology and immunology.

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting.. | 153 | $8,298,000 | 151 | $8,505,000 | -2 | +$207,000 |
| b. Competing..... | 4 | 248,000 | 4 | 258,000 | 0 | +10,000 |
| 2. Supplementals..... | (17) | 326,000 | (17) | 326,000 | 0 | 0 |
| 3. New..... | 7 | 329,000 | 7 | 349,000 | 0 | +20,000 |
| 4. Scientific Evaluation..... | (1) | 50,000 | (1) | 50,000 | 0 | 0 |
| 5. Total training grants..... | 164 | 9,251,000 | 162 | 9,488,000 | -2 | +237,000 |

Training Grants (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate..... | 164 | $9,201,000 | 162 | $9,438,000 | -2 | +$237,000 |
| 2. Scientific Evaluation..... | (1) | 50,000 | (1) | 50,000 | 0 | 0 |
| 3. Total training grants..... | 164 | 9,251,000 | 162 | 9,488,000 | -2 | +237,000 |

Training Grants Program Analysis

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Allergy and other Immunologic Disorders | 44 | $2,498,000 | 44 | $2,582,000 | 0 | +$84,000 |
| Bacterial and Mycotic Diseases | 43 | 2,405,000 | 43 | 2,517,000 | 0 | +112,000 |
| Parasitic Diseases | 23 | 1,295,000 | 21 | 1,233,000 | -2 | -62,000 |
| Viral and Rickettsial Diseases | 54 | 3,003,000 | 54 | 3,106,000 | 0 | +103,000 |
| Scientific Evaluation | (1) | 50,000 | (1) | 50,000 | 0 | 0 |
| Total training grants | 164 | 9,251,000 | 162 | 9,488,000 | -2 | +237,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 628 | $5,984,000 | 642 | $6,187,000 | +14 | +$203,000 |
| Other expenses | | 8,868,000 | | 8,955,000 | | +87,000 |
| Total | 628 | 14,852,000 | 642 | 15,142,000 | +14 | +290,000 |

Introduction

Objectives of the intramural research program are the discovery and exploitation of new knowledge for the better prevention or treatment of diseases caused by infectious agents or resulting from abnormal immunological reactions. The scope of the program is broad, embracing both basic and applied research on all aspects of a wide variety of diseases of infectious etiology including those caused by viruses, rickettsia, bacteria, yeasts, molds, fungi, protozoa and helminths; on various allergic and immune reactions to these agents and other antigens, and on such related problems as emphysema and the mechanisms of rejection of tissue transplants. Epidemiological, clinical, and laboratory approaches to these problems are constantly being modified by the new knowledge and technics deriving from the broad-based research programs in the medical and related sciences in this country and abroad. New viruses are discovered at intervals; the role of these and other newly discovered causes of human disease, such as mycoplasma, is being better defined and extended, new diagnostic methods evolved, and new technics of vaccination developed. Yet the large number of still unsolved problems provide ample evidence of the need for a continued vigorous multidisciplinary research effort to expand knowledge and to seek still undiscovered ways for earlier translation of the benefits of this expanding knowledge to the public benefit.

One of the properties of viruses and related obligate intracellular infectious agents (such as rickettsia) which has become increasingly clear during the past few years is that of persistence. New technics, developed in large part in the Laboratory of Viral Diseases, have shown that the infectious nucleic acid core of many viruses can persist in a state in which infectious virus particles are not produced for many generations of cell multiplication and replacement. These "latent" infections may be changed into "active" processes by many factors including climatological, biochemical, endicrinological changes, introduction of other infectious agents, and other natural or induced changes in the immunological status of the host. Herpes simplex or "cold sores" is the most common human example; but the relations between chicken pox in childhood and herpes zoster or "shingles" 40 to 50 years later, or of activation of cytomegalic virus during cancer chemotheraphy or immunosuppression for organ transplant are other examples of an increasingly important problem in medicine. Still more recently, the demonstration that several sarcoma viruses of animals exist in undetectable state in the tumor but can be converted into infectious sarcoma virus by adding the animal leukemia virus has shown how "helper" viruses can be used to detect these inapparent infections of cells and to open up new pathways for understanding how viruses or other intracellular parasites may cause a variety of chronic or degenerative diseases.

Still further advances in laboratory technology are needed before the etiologic agents of a number of common human diseases such as hepatitis and epidemic virus diarrheas can be isolated, identified, and used in vaccine development. New antiviral agents need to be identified and characterized as to their possible usefulness in prevention or treatment of a wide spectrum of viral diseases since vaccination can be only a partial public health answer to the hundreds of viruses capable of causing human infection.

The Institute continues to maintain field stations in Honolulu, Hawaii; Hamilton, Montana; Atlanta, Georgia; and the Panama Canal Zone. These stations enable the Institute to take advantage of the geographic differences in prevalence of certain diseases, to work more safely with these diseases in their natural ecological habitats or in animal populations which cannot be accommodated at Bethesda, or to take advantage of certain human volunteer populations for the study of malaria. Additionally the Institute has the scientific responsibility for research in cholera under the State Department Agency for International Development-Department of Health, Education, and Welfare agreement for the SEATO Cholera Research Program. This includes scientific responsibility for the SEATO-Pakistan Cholera Research Laboratory in Dacca, East Pakistan, where studies on the use of improved vaccines and new treatments for this scourge of the old world are being conducted. Exciting advances in the United States under NIAID grant support by the U.S.-Japan Cooperative Medical Science Program in coordination with the SEATO Program are those related to isolation of the cholera toxin which causes the fatal diarrhea and the development of vaccines for protection against this toxin. The SEATO-Cholera Research Program, using AID funding, is developing the toxins and vaccines for use in these studies both in the United States and in Pakistan, and plans the translation of beneficial results to man whenever appropriate.

Program plans in 1968 and 1969

Allergy and other Immunologic Disorders:

With the appointment of a new Clinical Director early in 1968, plans for the development of a broad based program of research on allergic disorders and chronic infections began implementation. These plans resulted from earlier decisions to alter and expand the clinical research program towards those problems which take full advantage of the unique facilities provided by the Clinical Center and which are difficult to conduct in the grant-supported university based research programs. Allergic disorders affect more than 20,000,000 Americans but, despite the rapid advance of medical science in many areas, are still little understood and are usually treated empirically. The closely related problem of immunological rejection of transplanted organs and tissues has been highly publicized and study of this phenomenon is a necessary part of research on allergy, as is the study of the genetically linked immunological disorders. The role of basic defects in the tissue immune or host resistance systems which permit establishment of chronic infections such as bronchitis or pyelonephritis is a second area of emphasis. The importance of these diseases in American medicine, and the difficulty of establishing broad and continuing programs in non-Federal facilities where the investigator must depend on short term grants and competitive use of clinical facilities for care of the sick and for research, make it necessary to undertake the program intramurally. Implementation of these programs will involve the addition of new investigator-level staff, renovations of existing space, new

equipment, and expanded research activities. When fully implemented, the program will not only provide a vital area of new research competence, but will train and add to the medical research community a group of investigators interested in and competent for research in allergy and chronic infections.

Paralleling the expanded and redirected effort in Clinical Investigation is the program of the Laboratory of Immunology. Under a newly recruited Laboratory Chief, who is an internationally recognized leader in immunological research including the problems of hypersensitivity, autoimmunity, and mechanisms of tolerance to antigenic stimuli, the program is expected to be complementary and closely correlated with the efforts on human disease problems in the clinical program. Because of the increased effort on clinically oriented problems and the broad program directed to basic immunological disorders and reactions of man, the proportionate staff of research trained physicians will be larger than had been previously required, with commensurate increases in costs.

To expand and implement these research programs for clinical allergy and immunology an increase of 9 positions and $200,000 is requested.

Viral, Mycoplasma and Rickettsial Diseases:

The virological research program is being reorganized to provide three major efforts. The Laboratory of Viral Diseases will be subdivided in 1968 to provide for a new laboratory concerned with the problems of respiratory virus and mycoplasmal diseases. The sections of the Laboratory of Viral Diseases which have been engaged in studies on the oncogenic properties of respiratory viruses that also have significance for oncogenesis in general, will be combined with the sections on viral biology from the Laboratory of Biology of Viruses and undertake the additional responsibility for a program of research on viruses as underlying causes of chronic and degenerative disease. This effort will relate to the program at the Rocky Mountain Laboratory on slow viruses, but will reduce the need to install a sophisticated virological competence at that laboratory by making it possible to take advantage of the animal models under study on the NIH site. The redirected laboratory effort will also relate to the programs of the Laboratory of Clinical Investigation on chronic bronchitis and other chronic infections since the deranged physiological activities induced by chronic viral infections may be an important underlying element. The Laboratory of Biology of Viruses will provide the capability for biochemical and biophysical studies of viruses at the molecular level which is a necessary component of the overall virological program in understanding the enzymatic and physiological changes induced by viral infections. Since the 1969 requirements for these reprogrammed efforts will be mostly met by present resources of the two laboratories, no specific increase in requested.

The "slow" virus research program at the Rocky Mountain Laboratory was scheduled for expansion in 1968 to take advantage of the animal facilities which were enlarged in 1967. This expansion was planned because of the importance of rapidly advancing efforts to isolate and identify in vitro this group of viruses which cause chronic progressive fatal diseases in animals as an essential step towards similar studies in man. Cost reductions have postponed this expansion at RML.

The research on arboviruses is being more sharply focused and concentrated at the Middle America Research Unit. While efforts at defining the Latin America hemorrhagic fevers continue to be productive and will be pursued, more emphasis is being given to vesicular stomatitis and other viruses which are common problems in North America. The special ecological environments available to MARU will enable it to define the ecology of vesicular stomatitis virus infections in various population groups and to learn the range of clinical illnesses which accompany this infection. Cooperative planning between the Middle America Research Unit, the Gorgas Memorial Laboratory and the Medical Entomology Section of the Rocky Mountain Laboratory on the research towards developing new methods for the control of encephalitis has been undertaken. The major need in the control of arbovirus infections is effective, safe vaccines. New approaches to inactivation of infectivity without loss of antigenicity are needed since conventional technics have often failed. There is also the need for discovery of more strains of virus in nature that have little ability to cause illness but which could be used to provide protection against the more pathogenic strains. The developing of attenuated strains in the laboratory and bringing them to human trial will at best be a long, difficult, and costly effort.

An increase of 5 positions and $125,000 is requested for these virological research programs.

Bacterial and Mycotic Diseases:

Work on killed tuberculosis vaccine will be maintained even though costs are increasing rapidly as the studies on immune processes progress through the necessary stages of studies from mice to higher animals before reaching man. Facilities at the Rocky Mountain Laboratory are not adequately safe to enable challenge of immunized primates with virulent mycobaterium tuberculosis strains, therefore these studies must be done in contract facilities. The increased costs will be met by reprogramming both at RML and elsewhere. No increase in costs are projected.

Still another parameter to the problem of antibiotic resistance of bacteria was added during 1967 when it was reported that episomal factors causing resistance to several antibiotics could be quickly transferred from resistant bacteria to previously susceptable bacteria even of different species. While the initial importance of this finding was directly related to enteric infections caused by gram negative bacteria, the discovery opened new pathways for the study of resistance in other micro-organisms and needs to be fully explored. Since these factors occur at the cellular level and the mechanism of action is so far undetermined, the primary efforts are in the area of bacterial genetics and the determinants of resistance. The work could be highly important to the study of chronic infections such as bronchitis because of the unresponsiveness of such infections to antibiotic therapy and the rapid emergence of resistant strains of bacteria in such cases which often create the worst problems of spreading hospital infections.

The involvement of intramural staff in research related to the disease categories identified under the U.S.-Japan program has increased the opportunities with corresponding pressures in research on such diseases as filariasis, schistosomiasis, tuberculosis and cholera. There are, however, no plans to increase the scope of commitment to research in these areas in 1968 and 1969.

The Institute will continue its efforts to develop better preventive, diagnostic and therapeutic methods for malaria. Vigorous research during the past few years on both human and monkey malaria has shown definitive immune responses to infection and an increased resistance to infection which appears to be long lasting. The major problem in approaching artificially induced immunity is that of the complex antigenic composition of the protozoa in the various stages of its life cycle and the complex interrelationships of the protozoa and tissue cells. The antigenic composition is being studied and related to specific immunoglobulin responses of patients infected, either as volunteers or naturally, with various strains of malaria. Concomitantly, there is research on the mechanisms involved in host eliminations of the parasite using the new opportunities which have been provided by simian malarias where species specificity enables strain selections which are eliminated with varying ease by the human host. Therapeutic evaluation of new drugs will also continue as these become available.

Renovation and updating of laboratories and equipment will continue as funds and opportunities permit. This is a continuation of a program begun in 1966 and directed toward the eventual replacement of obsolete laboratory furnishings and equipment. With the turnover of senior investigators, the necessary regroupings which accompany shifts in research emphasis as new senior investigators emerge or are employed, and the continued advancement in equipment saves time and expands capability for the scientist. Competing with laboratory equipment needs is the rapid growth of computer technology and the expanding requirements for funds to employ programmers and to obtain computer time.

Other programs of the Institute will continue at about the same levels as in 1968 with major changes being accomplished by reorientation.

Also included in the requested increases is $83,000 for the following mandatory items; annualization of 1968 pay costs and pay above the stated annual rate. There is also a decrease of -$118,000 for centrally furnished services from the "National Institutes of Health management fund."

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 33 | $347,000 | 33 | $354,000 | 0 | +$7,000 |
| Other expenses | | 10,676,000 | | 11,680,000 | | +1,004,000 |
| Total | 33 | 11,023,000 | 33 | 12,034,000 | 0 | +1,011,000 |

Introduction

The Collaborative Research and Development Program has as its mission the translation of significant basic research data into practical achievements of clinical applicability in allergy and infectious diseases. These activities are carried out primarily through research contracts with industry, universities, and other Federal and non-Federal institutions. In the planning and evaluation of contract-supported work the Institute is advised by committees comprised of leading scientists in the fields concerned. Each contract is monitored by a Scientist Project Officer, usually an NIH intramural research investigator, who reviews the scientific progress of the work and aids the contractors with special technical problems. In addition, an Administrative Project Officer is assigned to each contract to handle the non-scientific aspects of the project. The research areas encompassed by the Collaborative Research and Development Program are: (1) Transplantation and Immunology; (2) Research Reference Reagents; and (3) Virus and Bacterial Vaccine Development.

Program Plans in 1968 and 1969

Allergy and other Immunologic Disorders:

The primary mission of the Transplantation Immunology Program is to determine the importance in human organ transplantation of matching tissue antigens by typing. With the establishment of the program in 1965, the initial goal was to produce reagents necessary for human tissue typing tests.

During 1968, this goal was met to a degree far exceeding initial expectations. Substantial quantities of over 200 different tissue typing sera used in the matching of donors and recipients of organ transplants were produced. The characteristics of these sera have been listed in a catalog which is made available to interested immunologists. Good-quality antisera are now being redistributed to qualified laboratories. By the use of these reagents, rapid progress has been made in the identification of human transplantation antigens and tissue matching for kidney transplantation has become a reality in a number of clinics. The value of proper matching appears to be demonstrated in several small-scale prospective studies.

Conversely graft rejection was closely correlated with mismatches in a number of retrospective studies. During 1968, program efforts have resulted in the improvement of technical aspects of tissue typing with the result that it is now practical to conduct histocompatibility matching using small quantities of reagents. The Institute has established five regional tissue typing evaluation centers which actively participate in a program of prospective matching of donors and recipients for kidney transplants. These centers provide needed facilities in areas where kidney dialysis and transplantation programs are under way. Patients awaiting transplantation can now be typed prospectively. Methods have been established for rapid typing of cadaveric kidneys thus assuring the best possible match between the donor and recipient. Initial steps have been taken for immunological studies in recipients of transplanted tissue to determine the presence or recurrence of immunological disorders such as glomerulonephritis, auto-immune diseases, and incipient graft rejection.

During 1969, the program will be directed towards a large-scale evaluation of the efficacy of tissue typing in the selection of appropriate donors and recipients for transplantation. Facilities will be made available to type for kidney and other organ transplants. There will be a gradual reduction in the emphasis on reagents production with increasing emphasis on quality control and the establishment of a supply of stable, high-titered antisera which will be made available to immunologists engaged in clinical programs. The number of regional typing evaluation facilities will be increased and contractors will be asked to provide bench space and facilities to enable other workers to acquire increased proficiency in tissue typing techniques. Studies will be continued in delineating the patho-physiological changes which take place in kidneys during storage with the aim of producing more efficient methods for the preservation of kidneys. The typing evaluation centers will be closely integrated with the existing dialysis and surgical programs, organ procurement, and storage activities. Methods will continue to be explored to correlate programs which will permit investigators to work together -- partial funding to be obtained from other agencies and institutes.

Also during 1969, studies directed at achieving more efficient immunosuppression will be instituted. These include a study of candidate drugs discovered in the cancer chemotherapy program for immunosuppressive activity in patients, preliminary studies to develop more efficient and less toxic antilymphocyte sera, and studies to facilitate the production and evaluation of stable forms of tissue antigens which might be used to deminish the rejection reation. A program is also planned to provide for the collection of more useful and comprehensive data on transplant recipients. This program will provide information that can be used in the evaluation of data currently being collected on the results of tissue typings. Coordination with existing programs of the National Institute of Arthritis and Metabolic Diseases for the collection of data on dialysis patients will permit a more efficient analysis of the clinical course of patients who have been transplant failures and will provide additional data on the clinical background of new transplant patients formerly on dialysis therapy. An increase of $1,000,000 is programmed for these studies.

Viral, Mycoplasma, Bacterial and Rickettsial Diseases:

During 1968, the Vaccine Development Program is continuing its efforts in two major areas, (1) the development and testing of experimental rubella (German measles) vaccines and (2) the further development of vaccines against a mycoplasma and several viruses which are known to cause severe respiratory illness, and is initiating studies in two other promising areas: (1) the development and testing of streptococcal vaccines; and (2) the development and testing of vaccines for the prevention of pneumococcal pneumonia.

The rubella virus is recognized as an important cause of congenital defects such as heart disease, blindness and mental retardation in children born to mothers contracting German measles during pregnancy. Every effort is being directed toward the development of a safe, effective vaccine to prevent the occurrence of these congenital defects.

In 1968, an attenuated strain of rubella virus designated as HPV-77 developed by scientists at the Division of Biologics Standards has been extensively evaluated by clinical investigators in this country and abroad. Over 500 volunteers have been inoculated and approximately 450 susceptible individuals have been in contact with the vaccinees. None of the vaccinees or their contacts developed any illness attributable to the inoculation -- 96 percent of the vaccinees seroconverted. Although virus was shed from the nasopharynx, there was no evidence of transmission of the virus to the contact group.

Ideally, the rubella virus strain selected should be that which best meets all of the criteria for a safe and effective vaccine. These criteria include the following requirements: Inability to induce clinical illness and viremia; nontransmissability of the vaccine virus from vacinee to close contacts; lack of any appreciable shedding of vaccine virus from the pharynx; induction of high levels of serum antibody in recipients, and a life-long immunity to the natural disease; and ability of the vaccine strain to grow to high titer in a cell culture system acceptable for eventual administration to millions of children. HPV-77, the prime strain, fulfills most of the criteria. The small clinical trials which are now underway will be expanded to include larger numbers of vaccinees and controls.

In 1969, in addition to producing larger amounts of HPV-77 vaccine, the program will continue to explore HPV-77 derivatives propagated in other tissue culture systems such as canine kidney and duck and chick embryo.

The desirability of a killed rubella vaccine, particularly for women in the childbearing age group, is evident; however, work on developing an inactivated rubella vaccine has been discouraging. A number of physical and chemical agents have been employed to inactivate the virus. Although most agents used did inactivate the virus, they unfortunately also inactivated the virus' antigenicity. These studies will continue in 1969 to see if it is possible to completely inactivate the virus with the margin of safety that would be required and still maintain viral antigenicity.

During 1968, respiratory viruses vaccine development activities proceeded on a broad front. Extensive field trials of the adenovirus type 4 tableted vaccine have been conducted in the Armed Forces. Almost half a million military recruits received the oral vaccine during the past year. The vaccine continues to be about 90 percent effective in protecting against the natural disease. No untoward reations have occurred. The yearly financial savings to the Armed Forces in preventing acute respiratory disease is estimated at more than $10,000,000. Approximately the same amount of vaccine will be purchased by the Armed Forces during 1969.

Studies by two universities have confirmed the significance of Mycoplasma pneumoniae in causing pneumonia in civilian and military populations. Studies by other contractors have shown that the carrier state persists over several months or more, even in those with clinical illness adequately treated with the tetracyclines. Several prototype inactivated vaccines have been prepared which are extremely potent in animal model systems. However, the response in animals does not correlate well with the human response. Most of the Mycoplasma pneumoniae vaccines produced until now have been only about 50 percent effective. Work will continue in this field to study the development of potency test for Mycoplasma pneumoniae vaccines and to prepare concentration and fractionation of the antigens of Mycoplasma pneumoniae. In addition, the role of nutritional factors in the growth and antigenicity of Mycoplasma pneumoniae will be studied.

An inactivated trivalent parainfluenza vaccine was tested in children. Although the vaccine induced antibody in almost all vaccinees, it still did not protect against the disease. Improved vaccine preparations are now under clinical evaluation but no data are available at this time. A live attenuated respiratory syncytial (RS) virus vaccine has been produced and tried in adults. This live vaccine is capable of infecting adults without producing disease. Careful studies will be undertaken to observe the effect of this vaccine in children. Studies will continue including intranasal immunization in an effort to develop a vaccine effective against this most important pathogen of infancy. Work on the preparation of vaccine for the rhinoviruses which are the main known causes of the common cold will be increased. The rhinovirus typing program continues to be very successful. Through efforts of the program, fifty-five separate immunological types of rhinoviruses have been identified, characterized and accepted by the International Congress of Microbiology and the World Health Organization. Additional candidate rhinovirus strains have been submitted to the typing center and it is expected that the number of immunologically distinct rhinovirus types will approach one hundred. In 1968, several prototype inactivated rhinovirus vaccines will be clinically tested. Development of improved methodology for the assay of antibody response to rhinovirus infection will be pursued as well as the development of strains of rhinoviruses with attenuated virulence for humans, that may have promise as vaccine strains.

A program for the development of streptococcal vaccines is just beginning. During 1969, the further clinical evaluation of these vaccines will continue. The need for a safe and effective vaccine that could hopefully prevent strep throats and their serious long term complications such as rhuematic fever and glomerulonephritis is obvious.

In 1968, a program was instituted to develop and evaluate a polyvalent pneumococcal vaccine based on surveillance studies of pneumococcal disease incidence in those population groups which show high rish of morbidity and death from pneumonia. Despite antibiotic theraphy, pneumococcal infection continues to account for a significant number of the 55,000 or more "pneumonia and influenza" deaths per year which rank this among the ten leading causes of death in the United States - there is now evidence that this incidence is rising. In 1969, surveillance studies will be extended to other susceptible groups suitable for clinical evaluation of prototype vaccines; production of initial lots of vaccine for testing will also begin. An effective immunizing vaccine would not only lower the mortality rate, but should be a valuable step in combating the serious socio-economic problem posed by sharply rising hospitalization costs.

In 1968, the Reference Reagents Program has (1) completed reagents to most of the members of the adeno, myxo, entero, and herpes virus groups; (2) completed the production, testing and certification of eight arbovirus reagents, and eight of the human and animal mycoplasma reagents; (3) continued the production of human and animal mycoplasma reagents in a cooperative effort with the Division of Biologics Standards, and initiated a rhinovirus reagents production effort; (4) established five new contract projects for the production, testing and processing of both type specific and grouping reagents for arboviruses; and (5) distributed interferon reagents and entered a cooperative program with the World Health Organization for stability studies on mouse interferon.

In 1969, this program will (1) expedite the production, testing and distribution of much needed rhinovirus and arbovirus reference reagents; (2) continue the preparation of reagents to newly recognized enterovirus prototypes and make maximum use of the antiserum now on hand by preparing preliminary typing pools; (3) institute a systematic reexamination of research reference reagents now in the repository to confirm viability, titers, etc., and to determine presence of contaminants now detectable by methods not previously available, and to plan and initiate production of replacement reagents where indicated; (4) study and develop improved methodology in the production of antiserum, concentrating on such factors as the type and quality of animals used, the nature of antigens and adjuvants, immunization schedules and routes of injection; (5) develop and initiate production of immunoglobulin reagents for immunological research in virology; and, (6) initiate the production of research reagents to miscellaneous human viruses as well as other microbial agents of interest to the researcher or as needed by NIH intramural laboratories.

The Institute's Reference Reagents Program will continue to maintain close liaison with the National Communicable Diseases Center, World Health Organization, American Type Culture Collection and other groups with specific reagent programs to assure maximum coordination of effort and effective utilization of program funds as well as specific cooperative efforts to yield new information on reference reagents.

Included in this net increase is $7,000 for annualization of 1968 pay costs and $4,000 for services furnished centrally by the National Institutes of Health managment fund.

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Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 55 | $542,000 | 57 | $566,000 | +2 | +$24,000 |
| Other expenses | | 937,000 | | 938,000 | | +1,000 |
| Total | 55 | 1,479,000 | 57 | 1,504,000 | +2 | +25,000 |

This activity provides for the over-all coordination and administration of the Institute's grants programs. The activity is responsible for planning and developing scientific programs for research and training grants and fellowship awards. This involves the collection, processing, review and evaluation of applications; support of the National Advisory Allergy and Infectious Disease Council; liaison with appropriate organizations and scientists, continual vigilance by professional staff of program progress on scientific activities; and surveillance by supporting personnel on recording and reporting of varied information concerning grants management.

The requested program increase of $17,000 will provide for two additional positions for the grants management activity. The increase also includes $6,000 for annualization of 1968 pay costs and $2,000 for pay above stated annual rate.

Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 25 | $243,000 | 27 | $264,000 | +2 | +$21,000 |
| Other expenses | | 123,000 | | 141,000 | | +18,000 |
| Total | 25 | 366,000 | 27 | 405,000 | +2 | +39,000 |

This activity supports the Institute Director and his immediate staff in the over-all administration, coordination and direction of all the Institute's activities.

The requested program increase of $20,000 will provide for two staff positions. Also included are increases for annualization of the 1968 pay costs and $2,000 for pay above the stated annual rate. There is also an increase of $17,000 for centrally furnished services from the National Institutes of Health Management fund.

WEDNESDAY, MARCH 20, 1968.

# NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

## WITNESSES

DR. FREDERICK L. STONE, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
GORDON J. KLOVDAHL, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
MRS. EMMA LOU AKERS, BUDGET OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 1,731 | 2,093 | 2,187 |
| Positions other than permanent | 51 | 69 | 67 |
| Other personnel compensation | 13 | 17 | 16 |
| Total personnel compensation | 1,795 | 2,179 | 2,270 |
| Personnel benefits | 164 | 224 | 230 |
| Travel and transportation of persons | 154 | 183 | 210 |
| Transportation of things | 13 | 23 | 25 |
| Rent, communications, and utilities | 106 | 124 | 130 |
| Printing and reproduction | 6 | 143 | 142 |
| Other services | 114 | 105 | 112 |
| Project contracts | 3,525 | 3,525 | 3,513 |
| Payment to "National Institutes of Health management fund" | 1,654 | 1,749 | 1,863 |
| Supplies and materials | 55 | 65 | 84 |
| Equipment | 19 | 33 | 38 |
| Grants, subsidies, and contributions | 138,165 | 150,693 | 157,160 |
| Total obligations | 145,770 | 159,046 | 165,777 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 207 | 215 | 234 |
| Full-time equivalent of other positions | 5 | 7 | 7 |
| Average number of all employees | 185 | 212 | 228 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 75,030 | 84,054 | 88,886 |
| (b) Fellowships | 19,400 | 20,910 | 21,373 |
| (c) Training | 43,735 | 45,729 | 46,901 |
| Total grants | 138,165 | 150,693 | 157,160 |
| 2. Direct operations: | | | |
| (a) Collaborative research and development | 2,535 | 3,540 | 3,544 |
| (b) Training activities | 258 | 430 | 452 |
| (c) Review and approval of grants | 2,668 | 3,030 | 3,186 |
| (d) Program direction | 1,172 | 1,353 | 1,435 |
| Total direct operations | 6,633 | 8,353 | 8,617 |
| Total program costs, funded [1] | 144,798 | 159,046 | 165,777 |
| Change in selected resources [2] | 972 | | |
| Total obligations | 145,770 | 159,046 | 165,777 |
| Financing: | | | |
| Comparative transfer from other accounts | −965 | | |
| Unobligated balance lapsing | 283 | 1,204 | |
| New obligational authority | 145,088 | 160,250 | 165,777 |
| New obligational authority: | | | |
| Appropriation | 145,113 | 160,284 | 165,777 |
| Transferred to other accounts | −25 | −34 | |
| Appropriation (adjusted) | 145,088 | 160,250 | 165,777 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 145,770 | 159,046 | 165,777 |
| Receipts and other offsets (items 11-17) | −965 | | |
| Obligations affecting expenditures | 144,805 | 159,046 | 165,777 |
| Obligated balance, start of year | 94,967 | 110,847 | 141,780 |
| Obligated balance, end of year | −110,847 | −141,780 | −177,557 |
| Adjustments in expired accounts | −1,791 | | |
| Expenditures | 127,134 | 128,113 | 130,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 44,653 | 32,579 | 30,000 |
| Out of prior authorizations | 82,481 | 95,534 | 100,000 |

[1] Includes capital outlay as follows: 1967, $19,000; 1968, $33,000; 1969, $38,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $2,727,000; 1967, $3,699,000; 1968, $3,699,000; 1969, $3,699,000.

Mr. FLOOD. We now have the National Institute of General Medical Sciences, and the justification will be presented by Dr. Frederick L. Stone, the Director.

We have your biographical sketch here, which will be inserted in the record.

(The sketch follows:)

BIOGRAPHICAL SKETCH

Name: Frederick L. Stone.
Position: Director, National Institute of General Medical Sciences.
Birthplace and date: Biloxi, Miss.; March 31, 1915.
Education:
Middleburg College, Middlebury, Vt. (chemistry), B.S., 1937;
University of Rochester, Rochester, N.Y. (biology), M.S., 1942;
University of Rochester, Rochester, N.Y. (biology), Ph. D., 1948;
American University, Washington, D.C. (public administration), 1949–53.
Experience: Director, National Institute of General Medical Sciences, NIH, August 1964 to present; Chief, Division of Research Facilities and Resources, NIH, July 1962–August 1964; Acting Chief, Division of General Medical Sciences, NIH, January–July 1962; Assistant Chief, Division of General Medical Sciences, and Chief, Research Training Branch, DGMS, NIH, 1958–62; Assistant Chief, Division of Research Grants, and Chief, Research Training

Branch, DRG, NIH, 1957–58; Assistant to the Associate Director, NIH, 1956–57; director, Medical and Scientific Department, National Multiple Sclerosis Society, New York, 1955–56; assistant for professional services to the vice chancellor, Schools of the Health Professions, University of Pittsburgh, Pittsburgh, Pa., 1954–55; Chief, extramural programs, National Institute of Neurological Diseases and Blindness, NIH, 1951–54; Chief, Research Fellowship Branch, Division of Research Grants, NIH, 1948–51; instructor in biology, University of Rochester, Rochester, N.Y., 1947–48.

Association memberships: Member, Medical Advisory Board, National Multiple Sclerosis Society, New York, 1954 to present; consultant in basic medical sciences, Excerpta Medica Foundation, New York and Amsterdam, 1958 to present; member, Governing Board, Science Information Exchange, Smithsonian Institution, Washington, D.C., 1961 to present; consultant, Panel on Facilities, President's Commission on Heart Disease, Cancer and Stroke, Washington, D.C., 1964 to present; member, Jury 1965, 1966, and 1967 Albert Lasker Medical Research Awards.

Special awards, citations, or publications: Superior Service Award, Department of Health, Education, and Welfare, April 10, 1964; the Secretary's special citation, Department of Health, Education, and Welfare, January 1966.

Mr. FLOOD. I also see you have a statement, Doctor. How do you wish to proceed?

Dr. STONE. If it pleases you, sir, I would like to read the statement.

Mr. FLOOD. Proceed.

## GENERAL STATEMENT

Dr. STONE. Mr. Chairman and members of the committee: I welcome this opportunity to give you a progress report on the National Institute of General Medical Sciences, which was authorized by the Congress to foster, support, and coordinate research and training in a wide range of basic and clinical sciences.

### MAJOR SCIENTIFIC AREAS OF SUPPORT

The Institute has this past year clearly defined six major scientific areas for support: Pharmacology and toxicology as one unit, human genetics, biomedical engineering, clinical sciences, behavioral sciences, and those closely related sciences basic to an understanding of body functions.

These areas are being advanced through 1,500 project grants, 640 grants that support the training of 5,500 young scientists, and 2,200 fellowships awarded to young men and women of unmistakable promise.

The Institute is justly proud that its long support and encouragement of Dr. Arthur Kornberg and his associates at Stanford Medical Center were rewarded with the announcement last December that the team had produced a DNA virus capable of reproducing itself, creating in a test tube for the first time, the basic molecule of life, a notable achievement hailed throughout the world as a giant step toward the conquest of many human diseases and afflictions.

### PHARMACOLOGY AND TOXICOLOGY

The urgency and importance of the pharmacology and toxicology program is evidenced by the plethora of drugs in this country—more than 21,000 prescription drugs and tens of thousands of drugs sold without prescription in drug stores, supermarkets, and through the

mail. Yet the mechanisms of drug action and interaction in the body, as well as long term adverse effects, are vaguely understood. Studies supported by the Institute reveal the daily jeopardy of millions of persons who consume billions of doses of drugs, including alcohol.

Mr. FLOOD. Drugs, including alcohol?

Dr. STONE. It is considered a drug in a sense; in certain people it is sedative and at times has been listed as a mild anesthetic.

We know that age, sex, disease, and even behavioral patterns modify drug action, but we do not yet understand how. This past year, the Institute awarded grants for seven large-scale multidisciplinary research projects where these and many other drug problems are being investigated. Other projects concentrate on developing methods for evaluating the efficacy and safety of drugs, one of the most pressing needs in clinical pharmacology.

### BIOMEDICAL ENGINEERING

In biomedical engineering, the major effort of the past year was the support of scientists who are developing automated systems for use in hospital and other laboratories that conduct analyses for diagnostic purposes. Of particular promise is the automated laboratory system one of our grantees is perfecting and testing in a San Francisco hospital, a system that hospitals of all sizes could use and even small ones could afford.

### HUMAN GENETICS

With the control of infectious diseases and the correction of many metabolic disorders, more scientists are turning their attention to genetics, for a long time a wallflower of the health sciences, but dutifully attended by this Institute. Now classical human genetics is rapidly dividing into specialties, most recent of which are pharmacogenetics, the relation of a patient's genetic constitution to his response to drugs, and immunogenetics, largely in the field of organ transplantation which, so far, has been marked by surgical triumphs and chemical death due to genetic incompatibilities in tissues. The Institute's extensive genetics program embraces all aspects of that area of science. Among the grants awarded this past year were three to world-renowned geneticists whose scope extends from studies of molecular action to genetic aspects of whole populations.

### CLINICAL SCIENCES

This year, the Institute launched a national effort to stimulate research in the nature of trauma and ways of mitigating the effects of injuries and of speeding recovery in trauma victims. At the Institute-supported trauma center at the University of Cincinnati, physician-scientists are studying complications resulting from chest injuries in automobile accidents and from penetrating injuries of all types, wound contamination, and the control of infection in burns. At the Albany Medical College trauma center, a computer system is being developed to measure in seconds critical bodily changes that ordinarily take hours to measure, thus greatly increasing the chance of lifesaving treatment. From the subtlest chemical changes in body cells to the be-

havioral effects of trauma, studies are now underway in a concerted effort that will save numerous lives in a nation where injuries from all causes cost incalculable suffering and $15 billion a year.

ANESTHESIOLOGY

The increased interest among scientists in anesthesiology research was manifest in the high quality and number of requests for support of research and research training. The first anesthesiology research center grant was made to the University of Pennsylvania. Other grants for large, multidisciplinary projects were awarded to Northwestern and Harvard Universities. From these projects, we expect results that will benefit the 25 million patients who every year undergo surgery. A milestone was the new grant program to upgrade physician training in anesthesiology, a program which now supports some 80 specialists.

SUMMARY OF 1964 BUDGET REQUEST

Mr. Chairman, the appropriation request for the National Institute of General Medical Sciences for 1969 totals $165,777,000, an increase of $6,731,000 over the 1968 operating level of $159,046,000. Of the total increase requested, $4,832,000 is for research grants; $463,000 for fellowships; $1,172,000 for training grants; $4,000 for collaborative research and development; $22,000 for training activities; $156,000 for review and approval; and $82,000 for program direction.

I shall be happy to answer any questions.

Mr. FLOOD. General Medical Sciences. This reminds me of Rudyard Kipling's lines of tribute to the Irish guards. His son was killed, he was an officer of the Irish guards, and he wrote a tribute to the Irish guards which began by saying:

> We are not so old on the army list, but we are not so new at the game, and after 150 years we are fighting for France again.

You are not so old on the institutes list, are you, and obviously you are not so new at the game either.

You have an increase here of 112 in the number of research grants. This I can understand because you are a pretty new Institute, and you have an increase in projects coming up for continuation because few projects, relatively speaking, are being completed this year. As a matter of fact, you will actually be able to finance about 30 fewer new projects under this budget.

That is about right, is it not?

Dr. STONE. That is correct. Of the 112 additional projects, there will be fewer new ones than we had started last year, minus 30.

Your analysis was quite correct.

FELLOWSHIP AND TRAINING PROGRAMS

Mr. FLOOD. Here is something I do not understand.

The fellowship program aims at increasing the supply of trained personnel. You budgeted enough to increase this program a little. The training program has the same general objectives, but its budget goes the other way, not very much but it goes the other way. Why?

Dr. STONE. The general decision was made consistent with the sums of money available that the training grant program could this

year achieve its goal in a somewhat limited fashion with the sums of money available which as you pointed out, sir, result in a very small but a definite decrease in the number of programs.

Now, although there has been a decrease in the number of programs, there will be about the same number of people trained this year as last year.

MEDICAL SCIENTIST TRAINING PROGRAM

Mr. FLOOD. What about this medical scientist training program? Is this something new?

Dr. STONE. Within the large training grant program we have a small subprogram called the medical scientist training program. This program is very small and it is as yet experimental. There are only about four grants that are active.

The purpose of that subprogram is to provide support for young men who will at the same time undergo rigorous training in medicine and take the equivalent of the Ph. D. degree in most cases granted, but not a requirement.

This requires a commitment in advance of something between 6 and 7 years, which is longer than the normal commitment for medicine, which is 4. It is a very small subprogram of only four grants, involving somewhere between 60 and 80 trainees per year.

COORDINATION WITH OTHER INSTITUTES IN THE BEHAVIORAL SCIENCES

Mr. FLOOD. By the very nature of your Institute, General Medical, you cannot avoid overlapping with other Institutes to some degree. But in a couple of areas there seems to be a special problem. What is the division between you and the Mental Health Institute with regard to behavioral sciences?

Dr. STONE. In the first place, we have a very small program in the behavioral sciences. I am not avoiding the answer, but it is only fair to point out we have a very small program, it being the decision that the best thing for us to do at this time was to start in a very modest way, our Institute is new and has only recently been given clear responsibility.

Mr. FLOOD. What jurisdiction does the advisory council have on this?

Dr. STONE. The advisory council works in conjunction with the Director of NIH, and this has been decided, no objection I might say, by the advisory council on which Dr. Miller sits, who is an eminent psychologist from Harvard. If there is an overlap between the Mental Health Institute and our Institute, it would be, I believe, a relatively minor one because we hope and expect to support projects which intend to develop the behavioral sciences, as sciences, and this is the role that we play in providing large-scale support. Programs and projects of this nature will, I believe, cause no decided overlap with the Mental Health Institute, which is oriented toward the support of those projects and programs which directly relate into mental health and into psychiatry.

COORDINATION WITH FDA ON PHARMACOLOGY

Mr. FLOOD. What about coordination of activities in pharmacology between you and the Food and Drug Administration?

For instance, on page 17 you say you are the focal point for the

detection and study of adverse drug reaction. The FDA people make just as big a point of their adverse reaction reporting program. And the FDA receives substantial appropriations to run this program.

How do you put those two together?

Dr. STONE. There is no tension between us, you may be sure.

Dr. SHANNON. May I point out the striking difference between the two programs?

We are concerned with individuals who have an adverse drug reaction—and I'm trying to find out why they handle drugs in a sufficiently different manner to produce a reaction—rather than in just determining how much chance there is that a drug will produce a reaction. Some of our programs are specifically designed to discover the underlying mechanism. This is something the FDA does not touch. They are interested, before putting a drug on the market, in the reaction rate at a given dose that can be expected. This is not the purpose of our study.

Mr. FLOOD. You do not want to gild the lily, do you, Doctor?

Dr. STONE. No, sir.

HOSPITAL COMPUTER PROJECT

Mr. FLOOD. Let's talk about hardware.

Suppose you bring us up to date on your hospital computer project. When are you going to get that out of the research stage?

Dr. STONE. This is the hospital information I presume you are referring to, sir?

Mr. FLOOD. While you are at that, would you comment on automated clinical laboratories, also.

Dr. STONE. The particular project you first referred to at the Massachusetts General Hospital is one which we have supported for a number of years and will expect to be supporting. The problem has been to provide on-line capability and shared response in the computer system so that more than one, in fact several, physicians can use the system at one and the same time. The problem has been a sociological one, as well.

Mr. FLOOD. How long have you been at it?

Dr. STONE. The particular project you have in mind is now in its fourth year. And the problem of its usage is a sociological one. It is not a normal thing.

Mr. FLOOD. Sociological one?

Dr. STONE. Yes; as follows. It is not a normal thing for physicians and nurses to use a machine which involves a keyboard. They usually write out their orders in longhand and in the use of this machine they at the Massachusetts General and elsewhere had to develop specific kind of programs, the software, which would make this project a useful one.

Mr. FLOOD. This is part of the idea to get the nurses away from being choked to death on paper?

Dr. STONE. This would do it, but there are requirements to communicate in a way different from the normal way they have been used to doing. The project is one which we are reviewing at great length at the present time, and have just completed part of the review. The situation is one that, with the changing responsibilities in the Public Health Service we may very well enjoy joint support with another

unit of the Public Health Service that is able now to develop a greater base of support in what is called the hospital information service.

Mr. FLOOD. When are you coming in out of the kitchen with this research?

Dr. STONE. The group at Massachusetts General Hospital have provided more than the cost of the project several times over in consulting and providing hardware models, and general advice to, I think at least three, companies that have been concerned with the automation of hospital information services.

No one company has solved the problem as yet, but considering this has been supported by tax money, it has more than offset the cost. Much of the basic research, of course made available to the Nation, has been of use to the three companies. They are General Electric, Western Union, and International Business Machines.

### AUTOMATED LABORATORIES

If I may turn to the second question, which was the automated laboratory, the problem in automation of laboratories is twofold.

One is to develop the right kind of tests that are sensitive and accurate, and that can be run through in the minimum amount of time.

The second thing is to automate the process. The test is one thing and the automation is the other.

Now, the one particularly promising project is relatively small, as these projects go. It is operating in a hospital in San Francisco, a part of the University of California. Research has been going on to develop a system to combine the collection and calculation of data from laboratory instruments, and to transfer the results of the reporting media, and to allow the organization to put bookkeeping and laboratory work into a single reliable system rather than a series of manual steps that take place as tests are done. Into a reliable system that would substantially reduce the amount of time required.

Mr. FLOOD. We have all sorts of systems like that in the private sector and at the Defense Department; we have them on the battlefield at various command headquarters. We have all sorts of things like this, very miniaturized now in the third and fourth generation. They are very practical, we are told.

What is your problem?

Dr. STONE. They are trained to do a particular maneuver, they are not trained to go into a hospital laboratory nor are they trained to use the instruments there. It is one thing to talk about spin-off and the application of machines and devices that have been found useful in one field and their efficient use in another quite different field.

Miniaturization is nothing new, but as yet we are still in the research stage insofar as miniaturization can be applied to clinical pathology and to laboratory medicine generally.

The system is one in which they automate the analytical part of it, and then they automate the data requisition part. Unless you go into the two parts, in most laboratories you will find people running around marking things down by hand because there is a lack of equipment that makes it possible to take a blood sample here and get a printout there.

Mr. FLOOD. Why?

Dr. STONE. Partly the instruments have not yet been developed. And why? It is a lack of money and a lack of time and a lack of dedicated people, many of whom perhaps have only recently become interested.

Mr. FLOOD. The committee has sat here for several years now and listened to speeches and testimony on regional medicine.

They are going to have at the regional centers for heart, cancer, and stroke all of this hardware you tell us you cannot get and have not got the people to operate. Haven't we had automated laboratories for several years now?

Dr. SHANNON. You have not had those for several years, except in a very few cases. Such things as electrocardiographs have been automated for years, and many other things have been automated for years. But there is not available now general systems that will handle the bulk of biological measurements either in the patient's room, the operating room, or the laboratory.

What has just been said is perfectly correct: we have a large number of partially automated systems.

Mr. LAIRD. We are making pretty good progress along that line, though. We have some pretty automated systems.

Dr. SHANNON. We have them than can do five, 10, or 15 tasks. But the point I would make is that to make these generally applicable, providing them with a computer base and having them feed into an information system at the hospital—that you can get in probably 4 or 5 years, if you want it.

But, Mr. Flood, you cannot get it with the type of money you are putting in the budget today. This is going to limp along at a very slow rate for a very long period of time. This is probably the most expensive type of research to do. It involves very high priced industrial participation. It involves the same kind of people who are used in defense and aerospace. We do not have the kind of money that can purchase that type of service for this activity. You cannot be impatient about this because it is just not going to move that fast.

Mr. FLOOD. Are you sure?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Mr. Casey?

### COST OF AUTOMATION

Mr. CASEY. How much money do you think it will take?

Dr. SHANNON. We made an estimate last year and again this year. With an industry very eager to do this, its normal growth rate would be about $25 million a year for about 5 years and should then level off. This is how you really get results.

The problem is that in operating at these low budget levels you cannot get the best industrial brains to take the problem.

Mr. FLOOD. When there is gold in "them thar hills" we on the Defense Subcommittee find that they move in quite rapidly.

Dr. SHANNON. But Mr. Flood, for work of this sort we do not have the type of money to even touch the level of Defense contracts. It is just a different order of magnitude. Literally this is being done on a shoestring, when you really mark out the problem.

We have talked with industrial groups—Lockheed, United Aircraft, Aerospace Laboratory—and a number of them are extraordinarily anxious to get in this field, but with the funds available to us we cannot employ that type of skill. The thing we must realize is that, as the hospitals develop—in large measure stimulated by the

regional medical programs, in part stimulated by the progress in development of medicine itself—they will require, for the operation of an ordinary good community laboratory, some type of centralized facility for doing a wide variety of clinical measurements.

These small community hospitals, 200 beds or less, cannot afford to employ the technicians, cannot afford to employ the professional supervisors to make the many tests that are necessary for diagnosis or as to a guide to therapy.

The logical thing, and I do not believe anybody will gainsay this, is to set up centralized broad resources that hospitals can tap so that the most highly sophisticated techniques will be available not only to the university hospital but to the medium-sized community hospitals throughout an entire State.

Mr. CASEY. Taking it one step further, is it possible to make mobile what we call the ordinary basic physical operation where it could be moved around in communities? Where you cannot get the people to come to the facilities, take the facilities to them.

Dr. SHANNON. This would be particularly useful for screening procedures and the like. But the big need now is to develop comprehensive centralized laboratory resources to make these tests available to multiple and associated hospitals. These programs will not produce that type of laboratory. They may eventually, but not at a satisfactory rate. And they are going to be needed soon.

If we are going to develop the regional medical centers—heart disease, cancer, and stroke regions and subregions—you are going to need the hardware or it is not going to work. It will work, but not the way it is meant to.

Mr. FLOOD. Mr. Laird?

Mr. LAIRD. I do not believe I have any further questions.

Mr. FLOOD. Thank you, gentlemen.

JUSTIFICATION MATERIAL

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $160,284,000 | $165,777,000 |
| Transfer to "Community Health Services" | -34,000 | --- |
| Total | 160,250,000 | 165,777,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 12 | Research | | $84,054,000 | | $88,886,000 | | +$4,832,000 |
| | General research support grants | | (7,989,000) | | (8,127,000) | | (+138,000) |
| | Scientific evaluation grants | | (1,437,000) | | (1,437,000) | | (---) |
| | Pharmacology-Toxicology research | | (3,500,000) | | (3,500,000) | | (---) |
| | Anesthesiology and Diagnostic Radiology centers | | (1,000,000) | | (1,000,000) | | (---) |
| 20 | Fellowships | | 20,910,000 | | 21,373,000 | | +463,000 |
| 24 | Training | | 45,729,000 | | 46,901,000 | | +1,172,000 |
| | Direct operations: | | | | | | |
| 29 | Collaborative research and development | 2 | 3,540,000 | 2 | 3,544,000 | --- | +4,000 |
| 32 | Training activities | 30 | 430,000 | 30 | 452,000 | --- | +22,000 |
| 33 | Review and approval of grants | 124 | 3,030,000 | 139 | 3,186,000 | +15 | +156,000 |
| 34 | Program direction | 59 | 1,353,000 | 63 | 1,435,000 | +4 | +82,000 |
| | Total obligations | 215 | 159,046,000 | 234 | 165,777,000 | +19 | +6,731,000 |
| | Unobligated balance, reserve | 6 | 1,204,000 | --- | --- | -6 | -1,204,000 |
| | Total, obligations and reserve | 221 | 160,250,000 | 234 | 165,777,000 | +13 | +5,527,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 215 | 234 | +19 |
| Full-time equivalent of all other positions..... | 7 | 7 | 0 |
| Average number of all employees..... | 212 | 217 | +5 |
| Personnel compensation: | | | |
| Permanent positions..... | $2,093,000 | $2,187,000 | +$94,000 |
| Positions other than permanent..... | 69,000 | 67,000 | -2,000 |
| Other personnel compensation..... | 17,000 | 16,000 | -1,000 |
| Total personnel compensation..... | 2,179,000 | 2,270,000 | +91,000 |
| Personnel benefits..... | 224,000 | 230,000 | +6,000 |
| Travel and transportation of persons.... | 183,000 | 210,000 | +27,000 |
| Transportation of things..... | 23,000 | 25,000 | +2,000 |
| Rent, communications, and utilities..... | 124,000 | 130,000 | +6,000 |
| Printing and reproduction..... | 143,000 | 142,000 | -1,000 |
| Other services..... | 105,000 | 112,000 | +7,000 |
| Project contracts..... | 3,525,000 | 3,513,000 | -12,000 |
| Payment to "National Institutes of Health management fund"..... | 1,749,000 | 1,863,000 | +114,000 |
| Supplies and materials..... | 65,000 | 84,000 | +19,000 |
| Equipment..... | 33,000 | 38,000 | +5,000 |
| Grants, subsidies, and contributions.... | 150,693,000 | 157,160,000 | +6,467,000 |
| Total obligations by object..... | 159,046,000 | 165,777,000 | +6,731,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $160,284,000 |
| Transferred to "Community Health Services" | -34,000 |
| Unobligated balance, reserve | -1,204,000 |
| 1968 total estimated obligations | 159,046,000 |
| 1969 estimated obligations | 165,777,000 |
| Total change | +6,731,000 |

| Increases | Base Positions | Base Amount | Change from Base Positions | Change from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of new positions authorized in 1968 | --- | $ --- | --- | $28,000 |
| 2. Annualization of pay increase effective in 1968 | --- | --- | --- | 31,000 |
| 3. Additional day of pay in 1969 | --- | --- | --- | 8,000 |
| B. Program | | | | |
| 1. Research grants | --- | 84,054,000 | --- | 4,832,000 |
| 2. Fellowships | --- | 20,910,000 | --- | 463,000 |
| 3. Training grants | --- | 45,729,000 | --- | 1,172,000 |
| 4. Review and approval of grants | 124 | 1,707,000 | 15 | 60,000 |
| 5. Program direction | 59 | 974,000 | 4 | 23,000 |
| Total program increases | --- | --- | 19 | 6,550,000 |

| | Base | | Change from Base | |
|---|---|---|---|---|
| | Positions | Amount | Positions | Amount |
| Payment to "National Institutes of Health Management Fund" for centrally furnished services | | | | |
| Collaborative research and development | | $4,000 | | |
| Training activities | | 1,000 | | |
| Review and approval of grants | | 73,000 | | |
| Program direction | | 36,000 | | 114,000 |
| Total net changes requested | --- | --- | +19 | +6,731,000 |

Explanation of Changes

Research grants--The $4,832,000 program increase includes $4,694,000 for regular projects (noncompeting continuations, $4,694,000; competing projects, $2,844,000; offset by a decrease of $2,844,000 in new projects and supplementals) and $138,000 for general research support grants.

Fellowships--The program increase of $463,000 includes $76,000 for research career awards, $250,000 for special fellowships, and $137,000 for postdoctoral awards.

Training grants--The program increase of $1,172,000 reflects increases of $1,461,000 for noncompeting continuations, $361,000 for competing continuations and $50,000 for scientific evaluation, offset by decreases of $450,000 for new grants and $250,000 in supplementals.

Review and approval of grants--The program increase of $60,000 and fifteen positions will support the staff required to perform maximum evaluation of the grants programs.

Program direction--The program increase of $23,000 and four positions will strengthen the immediate staff in the Office of the Director, including staff for specialized program analysis.

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| 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 |

PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume IV.

"Sec. 442. The Surgeon General is authorized, with the approval of the Secretary, to establish in the Public Health Service an Institute for the conduct and support of research and research training in the general or basic medical sciences and related natural or behavioral sciences which have significance for two or more other institutes, or are outside the general area of responsibility of any other institute, established under or by this Act."

"Sec. 444. The Surgeon General shall, through an institute established under this part, carry out the purposes of sections 301 with respect to the conduct and support of research which is a function of such institute ...."

"Sec. 433. (a) .... In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions. The provisions of this subsection shall also be applicable to any institute established by any other provision of this Act to the extent that such institute does not already have the authority conferred by this subsection."

Explanation of Transfers

| | 1968 Estimate | 1969 Estimate | Purpose |
|---|---|---|---|
| Transfer to: | | | |
| "Community Health Services".. | $34,000 | - | Transfer of Scientific Evaluation Grant funds for support of Health Services Research Study Section. |

Justification

National Institute of General Medical Sciences

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 215 | $2,403,000 | 234 | $2,500,000 | +19 | +$97,000 |
| Other expenses..... | -- | 156,643,000 | -- | 163,277,000 | -- | +6,634,000 |
| Total..... | 215 | 159,046,000 | 234 | 165,777,000 | +19 | +6,731,000 |

General Statement

The National Institute of General Medical Sciences supports a broad base of fundamental and applied biomedical research activities aimed at the solution of certain major health problems. Specific programmed research objectives are to develop new knowledge for safer and more effective use of drugs, to understand the genetic basis of disease, to improve health services through the application of engineering knowledge to medical care; and to provide better diagnosis and therapy in medicine. The Institute also has principal responsibility for training young medical scientists in some 20 pre-clinical and clinical disciplines, thus reinforcing strongly the total National Institutes of Health research effort.

The National Institute of General Medical Sciences is requesting a total of $165,777,000 for F.Y. 1969, an increase of $6,731,000 over F.Y. 1968. This increase is to be used to sustain the support of research and training and increase the effort in existing programs of Clinical and Applied Sciences, Human Genetics and Sciences Supporting Applied Efforts.

RESEARCH GRANTS

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Regular program..... | $70,128,000 | $74,822,000 | +$4,694,000 |
| Special programs..... | 13,926,000 | 14,064,000 | +138,000 |
| Total research grants. | 84,054,000 | 88,886,000 | +4,832,000 |

Introduction:

The research effort of NIGMS is two-fold in scope. It consists in the support, first, of several areas of planned investigation which are designed to exploit opportunities for early application of research discoveries to major health problems and, second, of many independent research projects in diverse fields of science which in sum total provide the knowledge needed by applied, disease-oriented programs. These special areas include automation of clinical laboratories, trauma, pharmacology/toxicology, and human genetics. Development of a major program in each of these areas depends strongly on research results developed initially within small, independent research projects in various fields, the results of which can be brought to bear on a special problem or area.

For instance, study of gaseous transport and respiratory physiology has been important to the anesthesiology and surgery programs. Research discoveries in pharmacology, analytical chemistry and computer science have been important to both the automated clinical laboratories and the clinical pharmacology programs. Progress in biophysics, biomathematics and biochemistry has been essential to research on the technical developments in automated clinical laboratories, anesthesiology and trauma. The important programs and centers which are developing are combinations of clinical and multidisciplinary science programs. Several of these grew out of small or individual research projects whose initial support was begun by NIGMS.

Biomedical engineering, human genetics, pharmacology and toxicology are less clinically oriented programs which are, however, of increasing importance to the clinician. All of these programs have their roots in the fundamental science areas. Each may result in major advances in the treatment of specific diseases.

Program plans in 1968 and 1969:

The budget proposed for the coming year will sustain the support of research and increase effort in the existing programs to hasten the application of developments in biomedical science and clinical research areas to specific medical problems.

A number of awards have been made to highly qualified centers for research in the automation of clinical laboratories and to develop research programs in anesthesiology, radiology and trauma. The coming year will see these programs attain a significant level of productivity. Research efforts are expected to reveal ways of reducing the time and increasing the accuracy with which specimens are processed in the clinical diagnostic laboratory. Techniques for obtaining added information from diagnostic radiographic films are being developed and new insight is expected to be gained into the processes which cause death and disability in trauma victims.

Fiscal 1968 saw the test tube synthesis of a complete virus DNA by Dr. Kornberg of Stanford University. This major research advancement brings valuable insight into mechanisms associated with virus replication and has possible value in developing an understanding of phenomena such as the cancer process. Research in the pharmacology/toxicology program was stimulated by the opening of several new centers. The coordinated efforts of the project directors will allow this program to function as a national effort. The NIGMS pharmacology/toxicology research effort has already provided background information which will prove valuable in the extrapolation of research discoveries in animals to therapies for human illnesses. 1968 also saw the development of better methods for measuring the effectiveness and the required dose of drugs and for predicting the possible toxic reactions to drugs based on the genetic makeup of the recipient.

Since these applications include coordinated clinical and basic research in pharmacology and toxicology applications to clinical medicine will be hastened.

Clinical Sciences

Trauma - For the past several years the NIGMS has sought increasingly to stimulate and support research into the complex aspects of the therapy of trauma. Though previously little research has been done on this problem, the nation's fourth leading cause of death and disability, and the leading cause of disabling of young people between the ages of 1 and 35, the NIGMS has now started several centers for trauma research and has an additional 23 small research projects which are contributing in specific areas. Present major programs are concentrating on the metabolism of the injured patient, biochemical changes at the cellular level due to inadequate tissue oxygenation; infections as a sequela of burns or decreased resistance due to other major injury; the use of on-line computers for the constant assessment of severely injured patients; and other aspects of the pathology and

physiology of trauma. The smaller projects in addition to supplementing these studies are also concerned with different phases of shock, the repair of tissues and wound healing, rehabilitation, prosthetic devices and drowning. During the coming year, the Institute expects to review and hopefully to fund two or three more trauma research centers at a cost of $500,000 which will add significant strength to this program. The present support of trauma research is approximately $1,400,000. The economic return to the country from reducing the time of stay in the hospital, reducing costs of treatments, and decreasing the time required for rehabilitation of the traumatized patient, numbering the tens of thousands per year, cannot be overestimated.

Research in Genetics

The NIGMS program in Genetics seeks to improve health through understanding of the role of heredity in health and disease. It is estimated that in the United States more than a hundred thousand pregnancies end each year in miscarriage and that thousands of babies are born each year with such defects as mental retardation or abnormal anatomical and glandular development because of fetal chromosomal errors. Already evidence of cause and effect relationship between gene and action of specific diseases has been shown in a number of familial or inherited diseases. These include sickle cell anemia, Down's syndrome, cystic fibrosis, phenylketonuria, and others. It is in this area, and in the associated science underlying this area, that one of the most significant advances in Institute programs occurred this year. Nobel Laureate, Dr. Arthur Kornberg, announced the synthesis of biologically active DNA which enabled him to produce a product that acted exactly like a virus when introduced into living cells. This program is contributing valuable information in genetic factors which affect tissue and organ transplanation. The Institute's program is also concerned with chemical mutagenesis in the mammalian species. This refers to the ability of various chemicals in the environment to cause chromosomal aberrations in the same way that radiation or X-rays may damage the human reproductive process. Altogether, this program supports some 200 research projects covering the broad spectrum of genetics research including genetic chemistry, pharmacogenetics, and population genetics. The present level of support is approximately $8,000,000.

In 1969, we do not expect to appreciably increase the number of projects in this area; emphasis will be placed on selection of those projects which enhance and further the aims of this program, especially those areas of genetics research which can be applied directly to clinical problems.

Automated Clinical Laboratories

This program represents a concerted activity to bring chemistry and engineering knowledge and capabilities to bear on the information explosion in biochemistry and physiology as they relate directly to patient care. The program's purpose is to provide, through mechanical means, a more rapid and

more accurate analysis of biochemical and physiological data obtained from patients, and to provide the physician with reliable diagnostic data in a shorter time.

A next step in this process is expected to provide the physician automatically with an analysis of much of these data comparing by computer those chemical and physiological data which vary significantly with each other or with the normal.

A few years ago the armamentarium of the average hospital laboratory was some eight to ten clinical test procedures. Today this has been expanded to include several hundred tests on tissues, blood and other fluids. It is estimated now that the total number of annual tests in the United States is nearing one billion per year and it is expected to double within the next five years as it has over the past two decades. Present technology allows the "machine system" to make many simultaneous analyses for "routine" blood constituents. Experts in the field have advised the Institute that by improving, expanding and developing new instrumental approaches, hardware and software will be made available which should increase the laboratory capability by 15 percent to 20 percent by 1970 at a great savings of money and manpower.

Present programs are aimed at bringing much of this automation capability not only to large hospitals but also to the smaller hospitals where there are significant shortages of adequate automation to perform these tests and a severe limitation of trained personnel. These projects have been funded at a level of approximately $1,400,000 for the past two years, supporting sixty-one research projects and two contracts. Linked to this effort are thirty-eight specific research projects totaling $1,055,000 to provide essential understanding of new chemical techniques and methodologies which can be applied to further development. Modest expansion of the program will continue in the coming year with special emphasis on the development of automated analysis techniques.

Behavioral Sciences

Support of the behavioral sciences was assigned to this Institute because of their relation to other biomedical science disciplines and because research in the behavioral sciences provides information essential to the study of the inter-action of man and his surroundings. The present program consists of only ten projects investigating behavioral development, environmental adaptation and learning. The support of anthropological studies of populations is included in this category and is closely related to those projects in the genetics program concerned with population genetics. There are also three programs in the neurosciences which study behavior as related to function. Present support is $300,000, at the cellular and molecular level. Our plans are to increase support in this area to $400,000 during the coming year.

Supportive Basic Research

The NIGMS supports and encourages promising lines of investigation, utilizing the tools of the physical, biological, chemical, and mathematical sciences, which are concerned with the structure and function of living tissues and the processes of disease. These biomedical disciplinary programs are important to all of the Institutes.

The knowledge and information gained in the primary sciences permits explorations of mechanisms which can be applied to problems of medical significance. For example, promising lines of investigation in the physical sciences, computer technology, and chemistry lighted the way to engineering in biology and medicine and development of devices of patient monitoring, automated chemical tests in clinical laboratories, microelectronic devices for patient diagnosis, etc. To provide for coordination of this program and to guide it into the programs with targeted goals, a program director for biophysical sciences has been appointed.

Studies of living function are essential to all of the other programs; they provide the scientific rationale for these more applied missions. The kinds of research supported in this program are necessarily diverse since it is unrealistic to anticipate those scientific discoveries which might be applied to solving important medical problems. Therefore, the Institute supports programs that will increase information and advance knowledge on how cells react in disease states; studies in bioenergetics, which are related to problems of health and nutrition; and the chemistry and physics of cell function and structure in normal state and the disarrangements which occur in disease.

The programs in this area are a major unifying thread of research in the biological sciences and are focused at life processes studied on all levels of biological organization with the aim of elucidating the mechanisms and their control.

Pharmacology-Toxicology Research Centers

The Institute's Pharmacology-Toxicology Program seeks to improve human health through safer and more effective use of drugs. In recent years, pharmacology has produced many drugs and chemicals which have promoted the well being and comfort of millions of patients and have markedly altered the course of many diseases. On the other hand, the treatment of most types of cancer, heart disease, and stroke is still inadequate except for those situations where major surgery is feasible.

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There is a serious need for new medications for the metabolic diseases, the degenerative diseases such as arthritis, the allergic or hypersensitive conditions and for the treatment of trauma and injury. As rapidly as these

needs are met through production of new pharmacological products, the need for evaluation of possible adverse drug reactions and long-term effects is created. Knowledge obtained in this program is important to the medical profession and all the government agencies administering medical programs. Scientific research is necessary to provide information for safe use of drugs in the many disease oriented programs of the PHS where drugs are being applied and reviewed. This program is providing a focal point for the detection and study of adverse drug reactions.

During the past year several important developments have taken place. Methods have been developed and are being applied in study of the metabolism of a number of drugs, e.g. glutethimide, a sedative, guanethidine, an antihypertensive and related compounds, which show potential as therapeutic agents in hypertension. Application of chemistry methods such as gas chromatography and mass spectrometry to studies of drug metabolism in humans is being made. This is probably the most sensitive and specific methods of identification and analysis available and may reveal unsuspected toxic by-products or new useful compounds.

In the coming year further application of such methodology can be expected to lead to improved understanding of the effects of drugs and consequently more effective use of these materials. A particularly important study of the passage of drugs across the maternal--fetal barrier is planned. Such studies are of extreme importance in medication of pregnant women. New programs are also planned in molecular pharmacology to provide an understanding of how drugs react not only with the body cells and membranes but also with each other within the body. This is expected to reveal information on the causes of adverse drug reactions.

The present funding for the centers and projects in this area is $3,500,000. During the next year the existing centers will continue their development and new program projects specifically in the areas of maternal and fetal pharmacology, physical pharmacology and related areas will be developed.

Centers for Research in Anesthesiology and Diagnostic Radiology

As a result of testimony before Congress relating to the Heart Disease, Cancer and Stroke Program, it became apparent that major advances in the supporting specialties such as anesthesiology and diagnostic radiology would be essential to the conquest of these diseases. Therefore, the NIGMS was directed to stimulate research in these areas. In F.Y. 1968, $1,000,000 will be used for the development and support of a limited number of centers of excellence for research in these fields. To date two important centers in anesthesiology have been established utilizing fully the funds made available. Programs are being developed in diagnostic radiology but none yet have qualified as centers.

Anesthesia - The modern specialty of anesthesiology is concerned with far more than rendering a patient unconscious so that otherwise painful procedures can be carried out. The anesthesiologist because of his special combination of skills in clinical and underlying areas is concerned with all aspects of pain control, with the management of the unconscious patient from any cause, the treatment of respiratory emergencies, resuscitation, inhalational therapy, postoperative care, and many other problems. With full realization of the breadth and importance of this specialty, the NIGMS supports research in all its related areas as well as in the actual use and administration of anesthetics. Much of the research must be at original levels of pharmacology, respiratory physiology, and neurophysiology. Other research involves bioengineering approaches as in the development of automated anesthesia techniques. An important clinical area is concerned with obstetrical anesthesia and its effects on the newborn. This is still a major cause of natural death and infant distress. All of these areas are covered in the two new anesthesia research centers which have been established, and in the four active and highly productive program projects. They are further strengthened by our 30 individual projects concerned with specific aspects of the problem. There are good prospects for the development of at least three new major programs and several new smaller projects in F.Y. 1969.

Diagnostic Radiology - The central and essential role of diagnostic radiology in clinical medicine is well-known. The diagnostic radiologist functions primarily in the hospital setting where his service to every specialty creates a heavy work load which together with his need for very expensive, complex equipment makes research difficult. Nevertheless, new techniques and new approaches are essential if the radiologist is to meet the increasing demands for his services both in terms of the numbers of examinations required and the new types of procedures which should be developed.

At present, the NIGMS is supporting research in the techniques of the specialty including such special procedures as autoradiography and thermographic analysis of body heat radiation patterns to establish the existence of tumor, blocked blood vessels, or other abnormal conditions. The Institute also is supporting research on radioisotopes which will provide new instruments and computerized systems which will enhance greatly the radiologist's effectiveness in diagnosis using these valuable tools. One new project on a completely electronic emaging and recording system for X-rays permitting electronic reading of chest X-rays may have a tremendous effect on radiology practice in the future. Other programs which eventually will develop into a limited number of centers for research in diagnostic radiology have been programmed and are being considered at this time.

## Research Grants Program Analysis

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Clinical and Applied Sciences | $14,587,000 | $17,087,000 | +$2,500,000 |
| Human Genetics & other Biologic Control Systems | 19,986,000 | 21,486,000 | +1,500,000 |
| P/T and Medicinal Chemistry | 9,117,000 | 9,117,000 | -- |
| Sciences Supporting Applied Efforts | 26,438,000 | 27,132,000 | +694,000 |
| Subtotal regular program | 70,128,000 | 74,822,000 | +4,694,000 |
| General research support grants | 7,989,000 | 8,127,000 | +138,000 |
| Scientific evaluation and planning | 1,437,000 | 1,437,000 | -- |
| Pharmacology-Toxicology research | 3,500,000 | 3,500,000 | -- |
| Anesthesiology and diagnostic radiology centers | 1,000,000 | 1,000,000 | -- |
| Total research grants | 84,054,000 | 88,886,000 | +4,832,000 |

## Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting continuations | 1,120 | $49,883,000 | 1,200 | $54,577,000 | +80 | +$4,694,000 |
| 2. Competing projects | 189 | 8,708,000 | 251 | 11,552,000 | +62 | +2,844,000 |
| 3. Supplementals | (150) | 908,000 | ( 53) | 700,000 | (-97) | -208,000 |
| 4. New | 123 | 10,629,000 | 93 | 7,993,000 | -30 | -2,636,000 |
| 5. Subtotal regular program | 1,432 | 70,128,000 | 1,544 | 74,822,000 | +112 | +4,694,000 |
| 6. General research support grants | | 7,989,000 | | 8,127,000 | | +138,000 |
| 7. Scientific eval. & planning grants | | 1,437,000 | | 1,437,000 | | -- |
| 8. Pharm-Tox. research centers | | 3,500,000 | | 3,500,000 | | -- |
| 9. Anes. & Diag. Rad. centers | | 1,000,000 | | 1,000,000 | | -- |
| 10. Subtotal special programs | | 13,926,000 | | 14,064,000 | | +138,000 |
| 11. Total research grants | 1,432 | 84,054,000 | 1,544 | 88,886,000 | +112 | +4,832,000 |

FELLOWSHIPS

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total fellowships..... | $20,910,000 | $21,373,000 | +$463,000 |

Introduction:

Through its various fellowship programs, the National Institute of General Medical Sciences annually supports several hundred carefully selected scientists for research training in a broad spectrum of biomedical sciences. During F.Y. 1968, approximately 2,215 individuals will receive support under these programs in leading institutions throughout the country. All are working with mentors of proven competence and several, in fact, under the guidance of Nobel Laureates and other eminent leaders of the scientific world. It can be confidently expected that from this pool of scientific talent will emerge many outstanding biomedical investigators of the future. It is pertinent to note that a recent study of 300 of the Institute's former Research Career Development Awardees reveals that 50 percent are currently full professors or departmental chairmen at various universities throughout the Nation. An additional 30 percent have associate professorships, and most of the remainder hold responsible positions in research institutes or government laboratories.

Program plans in 1968 and 1969:

Predoctoral Fellowships - Basic to the several types of fellowships awarded is the large predoctoral program, which provides full-time graduate training leading to doctoral degrees in a wide variety of disciplines related to health.

Funds expended through this program represent a wise investment in our Nation's future, for it constitutes an important mechanism for assuring trained biomedical investigators to develop the application of basic findings to clinical medicine in the years ahead. During the current year, and in the coming year, support will be provided for some 1,430 predoctoral fellows, nearly one-third of whom can be expected to complete the requirements for their doctoral degrees annually.

Support is now provided for predoctoral fellows in approximately 120 institutions throughout the United States. Continued emphasis will be devoted during the coming year to achieving still broader institutional representation in this program while at the same time maintaining high standards of quality. In this endeavor, particular attention will be directed to the encouragement of fellowship support in departments to which training grants are unavailable. In addition, the program will be utilized to foster the training of additional graduate students in the areas of biomedical engineering, biophysics, genetics, and pharmacology-toxicology.

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Postdoctoral Fellowships - As the substance and methods of the biomedical sciences become increasingly complex, the need for research training beyond the formal graduate curriculum becomes more universal. Postdoctoral fellowships are designed to help meet this need, and from this program emerge young scientists qualified to conduct meaningful research in a wide variety of health-related fields.

Cognizant of the acute need for research manpower in pharmacology-toxicology as well as the increasing needs in biomedical engineering, biophysics, and genetics, staff effort will be devoted to the mounting of a more substantial program of postdoctoral training in these areas. Some emphasis will also be directed toward the support of additional postdoctoral fellows in the clinical sciences of anesthesiology, diagnostic radiology, and experimental surgery, although the major thrust in these areas will be provided through the programs of special fellowships and development awards.

The demand for postdoctoral fellowship support has increased markedly in recent years, and has far outstripped the number of available awards. Reaching a peak of 348 fellows in 1967, the number supported during the current year will be reduced to an estimated 271 due to an increase in stipend level and supply allowance. The increase of $137,000 requested in 1969 will permit a modest expansion of this program toward a level more commensurate with the need for postdoctoral training.

Special Fellowships - Special fellowships, which are characterized by a high degree of flexibility with respect to eligibility requirements, stipend levels, and duration of award, constitute an ideal mechanism for implementing the shifting emphases of the Institute's programmatic interests and responsibilities. Traditionally, these awards have been utilized primarily to support mature scientists in mid-career to take time from the pressures of regular professional responsibilities for the purpose of increasing or updating their research capabilities through advanced or specialized training. To an increasing degree, however, the Institute is emphasizing the special fellowship as a means of supporting young persons just emerging into scientific maturity. Thus, physicians who have just completed a residency and desire research training leading to a career in academic medicine, and young engineers who wish to enter the field of biomedical engineering are being supported in increasing numbers through this program.

Although still relatively small, the special fellowship program thus provides an important mechanism for fostering the training of highly selected individuals, with varied professional backgrounds, in fields of particular relevance to the mission of the Institute. During the current year, and in 1969, program emphasis will be focused on such areas as pharmacology-toxicology, biomathematics, biomedical engineering, biophysics and genetics, as well as on the selected clinical sciences of anesthesiology, diagnostic radiology and surgery. The increase of $250,000 requested for 1969 will permit a modest expansion of this program from the current level of 158 awards to an estimated 172 in the coming year.

Research Career Development Awards - Development awards are designed to foster the development of young scientists with oustanding research potential for careers of independent research in the sciences related to health. Through these awards, the Institute provides stable salary support (5 to 8 years) for some 300 talented young men and women during the crucial period of their careers when they are seeking to bring to fruition their capacity for independent investigation. From this program have emerged many individuals currently occupying senior positions in medical schools and other academic institutions, as well as in leading research institutes throughout the Nation.

Development awards, like special fellowships, are well adapted to the provision of advanced research training in clinical specialties as well as in scientific areas of particular importance to the mission of this Institute. Accordingly, during the current and coming year, continued programmatic effort will be devoted to the fields of anesthesiology, diagnostic radiology, and surgery, and also to the important areas of pharmacology-toxicology and genetics, and the interdisciplinary sciences of biomathematics, biomedical engineering, and biophysics.

Research Career Awards - Although new career awards are no longer being granted, provision must be made for the support of 40 ongoing awards. For this purpose, an estimated $1,256,000 will be required in F.Y. 1969.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations | | | | | | |
| a. Noncompeting. | 1,272 | $12,580,000 | 1,350 | $14,026,000 | +78 | +$1,446,000 |
| b. Competing.... | 91 | 1,302,000 | 112 | 1,450,000 | +21 | +148,000 |
| 2. Supplementals..... | (591) | 842,000 | (20) | 147,000 | -(571) | -695,000 |
| 3. New Awards..... | 852 | 6,186,000 | 787 | 5,750,000 | -65 | -436,000 |
| 4. Total fellowships. | 2,215 | 20,910,000 | 2,249 | 21,373,000 | +34 | +463,000 |

Fellowships (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Predoctoral..... | 1,430 | $7,947,000 | 1,430 | $7,947,000 | -- | --- |
| 2. Postdoctoral..... | 271 | 2,409,000 | 307 | 2,546,000 | +36 | +$137,000 |
| 3. Special..... | 158 | 2,160,000 | 172 | 2,410,000 | +14 | +250,000 |
| 4. Development Awards | 316 | 7,214,000 | 300 | 7,214,000 | -16 | --- |
| 5. Career Awards..... | 40 | 1,180,000 | 40 | 1,256,000 | -- | +76,000 |
| 6. Total fellowships. | 2,215 | 20,910,000 | 2,249 | 21,373,000 | +34 | +463,000 |

TRAINING GRANTS

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants... | $45,729,000 | $46,901,000 | +$1,172,000 |

Introduction:

The graduate training programs of the National Institute of General Medical Sciences are essential to achievement of the Nation's health research goals as well as those specific goals of the Institute. The development of a research program depends more upon the existence of adequately trained manpower than any other factor. As new areas of science develop and become clinically important, there must be manpower present and trained to exploit these applications and discoveries. The training of such persons must begin years in advance of the clearly anticipated need, since a minimum of seven years of training beyond the baccalaureate degree is necessary to produce a fully competent biomedical scientist.

From its inception the Institute has been responsible for the majority of the National Institutes of Health's program to develop new young health scientists. Research training programs currently aid some 4,500 predoctoral students on 637 different college and university grants. The number of students assisted has remained approximately constant over the past two years but the number of training grants has declined by 34. This decrease reflects a rise in the quality level of training programs as well as increased costs of research training in continuing programs supported by the Institute. Each research training grant award supports a number of students (trainees), enriches the research environment, and introduces apprentice researchers to broad perspectives of research under experiences and highly competent teachers. Research fellowships, by contrast, are administered on the basis of individual national competition but serve to complement training grants in several ways. At the predoctoral level, for example, they may be used to help support capable candidates in schools where formal training grant programs have not been established.

On a nationwide basis, Institute training grants support on the average more than 40 percent of the total national graduate enrollment in the fundamental health science disciplines, in some of which this ranges as high as 70 percent. This research manpower development program is thus able to substantially assist in determining both the scope and direction of the Nation's future health research effort and capabilities. Altogether, more than 25 biomedical and clinical science disciplines are supported which provide much of the research trained manpower necessary for the varied and continuing research programs central to the missions of the National Institutes of Health.

Experience over the past several years shows that about one-half the Institute-supported trainees and fellows will be recruited to research and academic positions in the Nation's medical schools where a large portion of NIH research-supported activities are conducted. This is most significant since a large number of academic positions are currently unfilled and projected needs for scientists to staff expansion of the Nation's medical education and research efforts over the next decade are still growing.

As intended and directed by the Congress, the Institute's manpower development program constitutes the Nation's most important single public support program for the training of medical scientists. These include the scientists who are needed now and who will be needed in increasing numbers for achievement of major research goals in areas of pharmacology and toxicology, biomedical engineering, biophysics, genetics, molecular biology, experimental psychology, and other behavioral sciences. The Institute is almost the sole source of support for training in research in general clinical areas, such as anesthesiology, diagnostic radiology, and general surgery. In a number of these areas where manpower needs are unusually urgent and where programmatic support is essential to the Institute's research missions, the Institute stimulates and supports special programs of research training.

Program plans in 1968 and 1969:

Because of the marked deficit in qualified researchers, and in those competent to train others, a special supplemental appropriation in F.Y. 1966 permitted the Institute to substantially increase the quantity and improve the quality of research training programs in surgery, diagnostic radiology, and anesthesiology. These programs continued to receive emphasis, although at a modest growth rate in F.Y. 1967 and 1968. This trend is expected to continue in F.Y. 1969.

Present indications are that trainees supported by existing grants in research anesthesiology will increase in number from 29 in 1966 to 69 in 1967 to 78 in 1968; in diagnostic radiology from 16 to 75 to 85 in the same period; and in surgery from 18 in 1966 to 127 in 1968. New training programs in clinical anesthesiology were launched in F.Y. 1967 to improve the quality of clinical care and bring the latest research innovations, after trial and evaluation, to the bedside. Approximately 80 postdoctoral and special trainees are enrolled in this program, which will be continued at the same levels in F.Y. 1968 and F.Y. 1969.

The Institute considers it important that emphasis be placed on increasing the number of full-time students working toward a definite career goal. As a result, training programs support only full-time trainees on stipends.

Medical Scientist Program

The objective of the Medical Scientist Training Program is to assist universities and their medical schools in the development of flexible, individualized programs of combined medical and scientific training for highly-motivated

trainees of superior research and academic potential. The grants are institutional in nature, and permit trainees to draw upon the full range of academic, scientific, and related opportunities. Medical Scientists, upon the completion of training, will differ from most scientists in having had the background of medical training required to investigate direct clinical problems of disease in man. They will differ from most clinicians in having had extended research experience and the essential background in appropriate combinations of the physical, biomedical, and behavioral sciences needed to bring the fundamental knowledge of these disciplines into clinical research. It is estimated that approximately 200 individuals with such combined training are needed each year for the next decade. This program now consists of 6 grants with funds which total approximately $1,500,000 and which support approximately 112 trainees, each enrolled in a six-year program. The first 15 trainees in these programs are expected to graduate in 1970.

The funds requested in 1969 will permit the continuation of 611 high-quality training programs. At the same time, 26 programs of lesser merit will be discontinued. Because of increased costs of living, the 611 continuing programs will cost more than the 637 programs supported in F.Y. 1968. In addition, three new training grants will be made. All of the requested increase will be devoted to meet committed increases in the medical scientist and clinical research training areas.

Training Grants Program Analysis

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Anatomical sciences..... | 41 | $2,450,000 | 40 | $2,450,000 | -1 | --- |
| Anesthesiology..... | 14 | 1,120,000 | 14 | 1,170,000 | - | +$50,000 |
| Clinical Anesthesiology. | 30 | 1,000,000 | 30 | 1,000,000 | - | --- |
| Behavioral sciences..... | 32 | 2,400,000 | 30 | 2,400,000 | -2 | --- |
| Biochemistry..... | 71 | 5,300,000 | 68 | 5,300,000 | -3 | --- |
| Biomedical engineering.. | 17 | 1,400,000 | 16 | 1,400,000 | -1 | --- |
| Biometry..... | 30 | 2,300,000 | 29 | 2,300,000 | -1 | --- |
| Biophysical sciences.... | 30 | 2,700,000 | 29 | 2,700,000 | -1 | --- |
| Epidemiology..... | 10 | 750,000 | 10 | 750,000 | - | --- |
| Genetics..... | 34 | 2,820,000 | 34 | 2,820,000 | - | --- |
| Medical scientist..... | 6 | 1,429,000 | 7 | 1,877,000 | +1 | +448,000 |
| Microbiology..... | 51 | 2,530,000 | 48 | 2,530,000 | -3 | --- |
| Multidisciplinary and special programs..... | 32 | 3,420,000 | 31 | 3,420,000 | -1 | --- |
| Nutritional sciences.... | 13 | 650,000 | 12 | 650,000 | -1 | --- |
| Pathology..... | 59 | 3,710,000 | 56 | 3,710,000 | -3 | --- |
| Pharmacology and Toxicology programs.... | 70 | 4,650,000 | 66 | 4,694,000 | -4 | +44,000 |
| Physiology..... | 50 | 2,780,000 | 47 | 2,780,000 | -3 | --- |
| Diagnostic Radiology.... | 21 | 1,760,000 | 21 | 2,100,000 | - | +340,000 |
| Surgery..... | 26 | 2,260,000 | 26 | 2,500,000 | - | +240,000 |
| Scientific evaluation and planning..... | (2) | 300,000 | (2) | 350,000 | - | +50,000 |
| Total training grants | 637 | 45,729,000 | 614 | 46,901,000 | -23 | +1,172,000 |

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting..... | 539 | $37,000,000 | 511 | $38,461,000 | -28 | +$1,461,000 |
| b. Competing..... | 86 | 7,429,000 | 100 | 7,790,000 | +14 | +361,000 |
| 2. Supplementals..... | (10) | 400,000 | (10) | 150,000 | -- | -250,000 |
| 3. New programs..... | 12 | 600,000 | 3 | 150,000 | -9 | -450,000 |
| 4. Scientific evaluation and planning..... | (2) | 300,000 | (2) | 350,000 | -- | +50,000 |
| 5. Total training grants | 637 | 45,729,000 | 614 | 46,901,000 | -23 | +1,172,000 |

Training Grants (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate..... | 607 | $44,429,000 | 584 | $45,551,000 | -23 | +$1,122,000 |
| 2. Clinical Training Anesthesiology..... | 30 | 1,000,000 | 30 | 1,000,000 | -- | --- |
| 3. Scientific evaluation and planning..... | (2) | 300,000 | (2) | 350,000 | -- | +50,000 |
| 4. Total training grants | 637 | 45,729,000 | 614 | 46,901,000 | -23 | +1,172,000 |

COLLABORATIVE RESEARCH AND DEVELOPMENT

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 2 | $11,000 | 2 | $20,000 | -- | +$9,000 |
| Other expenses..... | -- | 3,529,000 | -- | 3,524,000 | -- | -5,000 |
| Total..... | 2 | 3,540,000 | 2 | 3,544,000 | -- | +4,000 |

Introduction:

This activity supports by contract research projects that are both developmental and applied in nature and directed toward the mission of this Institute. Current programs supported by this activity include: (1) Automated Laboratory Medicine; (2) Pharmacology-Toxicology; (3) Genetic Chemistry; (4) Hospital Computer Project; and (5) Studies and Projects Conducted by the National Academy of Sciences.

Program Plans in 1968 and 1969:

Automated Laboratory Medicine

This program will provide the means whereby the most recent advances in medical laboratory science may be applied to the practice of preventive, diagnostic and therapeutic medicine as well as to the evaluation of individual and public health through the design and development of automated clinical laboratory equipment.

Increasing numbers of clinical laboratory procedures are being demanded for diagnostic purposes. Recent studies indicate that the number of tests performed in the hospital laboratory has increased 10-15 percent per year since 1955 and there is no indication of a leveling off of this trend in the foreseeable future.

In addition to the problem of handling the massive amount of data now obtained on each hospital patient, other serious problems are created by the increasing number and complexity of tests. The solution to the clinical laboratory problem rests in: the automation of current laboratory procedures; development of new procedures which can be automated; invention of devices which can accept samples and produce finished results in a short time with high reliability, reproducibility and sensitivity; use of computer technology to control processing; recording of results; and print-out of data. Other advantages to development of automation to its maximum extent would be: a

reduction in the time elapsed from receipt of a sample to delivery of information to the physician from days or hours to minutes; rapid diagnosis by providing computer output of all tests performed on each patient on a single print-out sheet; identification of abnormal test results by computer program; and consecutive read-out of past tests, as a profile, to identify trends in patient response.

Although the largest portion of this program is supported by grants, two contracts totaling $500,000 are being supported in the current year in this field. These contracts are largely for the purpose of automating analysis of steroids and urinary constituents. The 1969 estimate provides for continuing this program at the same level.

Pharmacology/Toxicology

This program provides by contract support of collaborative studies designed to develop information in specific areas, such as: (1) study of widely used sedatives which may interfere with the beneficial and occasionally life-saving action of other drugs frequently prescribed for the treatment of acute coronary thrombosis (heart attack); (2) study of drugs given for the treatment of serious illness which may appear to have failed in certain patients not because of the inadequacy of the drug, but because of inability to achieve the necessary blood levels or concentrations in the average person; (3) study of drugs which may at times have very serious adverse side effects. In 1968 this program is being supported at a level of $1,000,000 and the 1969 estimate provides for a program at the same level.

Genetic Chemistry

The objectives of this program are to understand the functions of genetic material; to determine the specific sites in the molecule which determine genetic activity; and to find appropriate ways of possibly altering genetic functions to correct defects producing disease states. In an attempt to solve this problem the Institute has contracts with the Oak Ridge National Laboratory for research on methods of separation, purification, and isolation of pure ribonucleic acids (RNA) and specific enzymes, for isolation of large quantities of pure RNA on pilot-plant scale, and provision of these biomacromolecules so that chemical analyses and structure details may be determined. To date, this research has succeeded in devising novel separations technology for the isolation, in several-hundred milligram quantities, of a few kinds of pure s-RNA's for distribution to prominent geneticists.

This program is supported at a level of $800,000 during 1968 and 1969.

Hospital Computer Project

The Hospital Computer Project is being supported in 1968 and 1969 at $800,000 by contract. This project involves the development of a computer-based hospital information system to process clinical research data, including

REVIEW AND APPROVAL OF GRANTS

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 124 | $1,395,000 | 139 | $1,458,000 | +15 | +$63,000 |
| Other expenses..... | --- | 1,635,000 | --- | 1,728,000 | -- | +93,000 |
| Total..... | 124 | 3,030,000 | 139 | 3,186,000 | +15 | +156,000 |

This activity supports professional and supporting staff required for the planning, direction, review, analysis and overall management of three specialized grant programs, research grants, training grants and fellowships. This activity also supports the National Advisory General Medical Sciences Council.

The program increase of $60,000 and fifteen positions will provide for gradual recruitment of highly specialized staff to perform more extensive review and evaluation of grant applications with increased surveillance of nationally emphasized program areas. Included in the net increase is $18,000 for annualization of pay increases effective in 1968, and $5,000 for one additional day of pay in 1969.

There are also increases of $73,000 for centrally furnished services from the "National Institutes of Health Management Fund".

PROGRAM DIRECTION

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 59 | $690,000 | 63 | $694,000 | +4 | +$4,000 |
| Other expenses..... | -- | 663,000 | -- | 741,000 | -- | +78,000 |
| Total..... | 59 | 1,353,000 | 63 | 1,435,000 | +4 | +82,000 |

This activity supports the overall administration and direction of the programs of the Institute which includes the Office of the Director and the Program Analysis Branch.

The program increase requested of $23,000 and four new positions will provide staff necessary to meet requirements for increased emphasis in the compilation of data on Institute programs and preparation of interpretative reports.

Included in the net increase is $11,000 for annualization of positions new in 1968, $2,000 for an additional day of pay in 1969, and $10,000 for annualization of pay increase effective in 1968, offset by increase in lapsed employment of $19,000.

There are also increases of $36,000 for centrally furnished services from the "National Institutes of Health Management Fund".

THURSDAY, MARCH 21, 1968.

# NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

## LIST OF WITNESSES

DR. GERALD D. LaVECK, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
CALVIN B. BALDWIN, JR., EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
EARL M. HUBSCHER, BUDGET OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 2,976 | 3,488 | 4,273 |
| Positions other than permanent | 66 | 99 | 102 |
| Other personnel compensation | 59 | 83 | 100 |
| Total personnel compensation | 3,101 | 3,670 | 4,475 |
| Personnel benefits | 336 | 401 | 465 |
| Travel and transportation of persons | 195 | 271 | 320 |
| Transportation of things | 45 | 46 | 56 |
| Rent, communications, and utilities | 161 | 140 | 185 |
| Printing and reproduction | 5 | 86 | 95 |
| Other services | 870 | 653 | 700 |
| Project contracts | 2,445 | 2,957 | 6,349 |
| Payments to "National Institutes of Health management fund" | 2,485 | 2,733 | 3,378 |
| Supplies and materials | 227 | 228 | 252 |
| Equipment | 953 | 539 | 649 |
| Grants, subsidies, and contributions | 53,595 | 56,311 | 58,470 |
| Total obligations | 64,418 | 68,035 | 75,394 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 430 | 478 | 573 |
| Full-time equivalent of other positions | 12 | 13 | 13 |
| Average number of all employees | 356 | 407 | 521 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimated | 1969 estimated |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 40,592 | 42,447 | 44,265 |
| (b) Fellowships | 3,724 | 4,102 | 4,193 |
| (c) Training | 9,279 | 9,762 | 10,012 |
| Total grants | 53,595 | 56,311 | 58,470 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 3,828 | 5,098 | 6,693 |
| (b) Collaborative research and development | 1,158 | 1,530 | 5,032 |
| (c) Biometry, epidemiology, and field studies | 1,353 | 2,040 | 2,046 |
| (d) Training activities | 47 | 89 | 89 |
| (e) Review and approval of grants | 1,646 | 1,954 | 1,986 |
| (f) Program direction | 871 | 1,013 | 1,078 |
| Total direct operations | 8,903 | 11,724 | 16,924 |
| Total program costs, funded [1] | 62,498 | 68,035 | 75,394 |
| Change in selected resources [2] | 1,920 | | |
| Total obligations | 64,418 | 68,035 | 75,394 |
| Financing: | | | |
| Comparative transfers from other accounts | −2,181 | | |
| Unobligated balance lapsing | 2,685 | 586 | |
| New obligational authority (appropriation) | 64,922 | 68,621 | 75,394 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 64,418 | 68,035 | 75,394 |
| Receipts and other offsets (items 11-17) | −2,181 | | |
| Obligations affecting expenditures | 62,237 | 68,035 | 75,394 |
| Obligated balance, start of year | 39,237 | 42,155 | 49,190 |
| Obligated balance, end of year | −42,155 | −49,190 | −61,584 |
| Adjustments in expired accounts | −1,059 | | |
| Expenditures | 58,260 | 61,000 | 63,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 22,907 | 24,000 | 25,000 |
| Out of prior authorizations | 35,353 | 37,000 | 38,000 |

[1] Includes capital outlay as follows: 1967, $429,000; 1968, $539,000; 1969, $649,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $2,013,000; 1967, $3,934,000; 1968, $3,934,000; 1969, $3,934,000.

Mr. FLOOD. The subcommittee will come to order.

We now have the National Institute of Child Health and Human Development. The presentation will be made by Dr. Gerald D. LaVeck, the Director.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESSES

We have a biographical sketch of the doctor which will be placed in the record at this point.

(The biographical sketch follows:)

Name: Gerald D. LaVeck, M.D.
Position: Director, National Institute of Child Health and Human Development.
Birthplace and date: Seattle, Wash., April 19, 1927.
Education:
1948: B.S., University of Washington, Seattle.
1951: M.D., University of Washington School of Medicine.

Experience:

1967–present: Clinical professor of pediatrics, Georgetown University School of Medicine.
1966–present: Director, National Institute of Child Health and Human Development.
1966–67: Acting Scientific Director, National Institute of Child Health and Human Development.
1965–67: Clinical associate professor in prediatrics, Georgetown University School of Medicine, Washington, D.C.
1963–66: Director, mental retardation program, National Institute of Child Health and Human Development.
1962–63: Head, Chippled Children's Service, Washington State Department of Health.
1961–62: Clinical director, Rainier School, Buckley, Wash.
1963: Clinical associate professor of pediatrics, University of Washington School of Medicine.
1960–63: Clinical assistant professor of pediatrics, University of Washington School of Medicine.
1958–60: Instructor in pediatrics, University of Washington School of Medicine.
1958–61: Medical director, Rainier School, Buckley, Wash.
1957–58: Instructor in pediatrics and fellow in mental retardation, University of Washington School of Medicine, Department of Pediatrics, Neurology, and Neuropathology.
1956–57: Resident, pediatrics, Children's Orthopedic Hospital, Seattle, Wash.
1955–56: Assistant resident, pediatrics, Child Health Center and King County (Wash.) Hospital.
1953–55: Senior assistant surgeon, U.S. Public Health Service, Epidemic Intelligence Service, Communicable Disease Center, Atlanta, Ga.
1952–53: Resident, public health, Seattle King County Department of Public Health.
1951–52: Intern, rotating, Vancouver General Hospital, Vancouver, British Columbia.

Association memberships:

Diplomate, American Board of Pediatrics.
Fellow:
American Academy of Pediatrics.
American Public Health Association.
Member:
American Medical Association.
American Association on Mental Deficiency.
American Association for the Advancement of Science.
Washington State Medical Association.
Thurston County (Wash.) Medical Society.

Special awards, citations, or publications:

Superior Service Award, U.S. Department of Health, Education, and Welfare, April 1966.
Numerous papers and book contributions relating to infectious diseases, and mental retardation

Mr. FLOOD. How long have you been the Director, Doctor?

Dr. LAVECK. Since October 1966; 17 months.

Mr. FLOOD. You may proceed, Doctor.

## GENERAL STATEMENT

Dr. LAVECK. Mr. Chairman and members of the committee; the National Institute of Child Health and Human Development seeks to obtain a better understanding of the biological and behavioral aspects of human development from the beginning to the end of life. We want all children to be born healthy, to survive their infancy, to grow up without handicaps, and to achieve their maximal potential. Important specific objectives include the reduction of infant mortality

and the development of a sound scientific base for realistic family planning practices. We must be concerned with the process of intellectual development and understand the aging process.

INFANT MORTALITY

In 1967, more than 78,000 infants in the United States died during the first year of life—an infant mortality rate of 22.1 per 1,000 live births, or a drop of 6 percent in comparison with 1966. This represents the most significant drop in infant death rates in over a decade. We have found diet, drugs, environmental influences, heredity, maternal illnesses and social factors can have a profound effect on the well-being of the unborn child. But much more research is needed before we know the precise influence of these and other factors on the outcome of pregnancy.

ANTI-RH PREPARATION

However, one health hazard to many infants, the presence of Rh blood incompatibility, which has caused the deaths of approximately 5,000 infants per year, may be eliminated in the next few years as a result of Institute-supported research. An anti-Rh preparation designed to prevent a mother with Rh-negative blood from becoming sensitized to her infant's Rh-positive blood has been developed and used successfully in a large number of cases. This preparation will soon become generally available.

Mr. FLOOD. In the next few years? What do you mean by a "few?"

Dr. LAVECK. We are waiting for the product I just mentioned to be approved by the Division of Biologics Standards. This approval should come shortly.

Mr. FLOOD. What does "shortly" mean?

Dr. LAVECK. In talking to Dr. Murray, it appears that the product will be approved within the next month or two. When this product is widely available, we eventually will see a decline in and perhaps the elimination of this particular problem.

Mr. FLOOD. Is it expensive?

Dr. LAVECK. Not particularly. I do not have the information on the exact cost but it might not cost more than $65.

Mr. FLOOD. Is that expensive?

Dr. LAVECK. Not when you consider the problem that is involved.

Mr. FLOOD. It will be available under what circumstances?

Dr. LAVECK. It will be available to the private practicing physician.

An anti-Rh preparation designed to prevent a mother with Rh-negative blood from becoming sensitized to her infant's Rh-positive blood has been developed and used successfully in a large number of cases. This preparation will soon become generally available.

Mr. FLOOD. What does "sensitized" mean?

Dr. LAVECK. The problem arises when the mother is Rh-negative and the fetus is Rh-positive. Maternal antibodies are produced which destroy the infant's red blood cells.

Mr. FLOOD. What is the word?

Dr. LAVECK. Rh refers to a factor that may be present in red blood cells.

Mr. FLOOD. Dr. Shannon, what does the term "sensitized" mean generally?

Dr. SHANNON. Generally speaking, it is the development of a tendency to react to external material in substantially smaller quantities than normally is the case. It would be like you or I saying that a man is sensitive. You mean that he takes objection to minor slights and blows them up as though they were very important episodes. Biologically, it means precisely the same thing; that amounts of external material that in the normal individual would produce essentially no reaction, in the sensitized individual result in a large flareup and a profound reaction that may make the individual quite ill, either locally or generally. It really is the meaning you normally use in your daily conversation.

Mr. FLOOD. With reference to you, what does the Rh mean?

Dr. LAVECK. The Rh factor is a particular factor found in the red blood cells of humans that was originally identified in the Rhesus monkey. About 85 percent of the white population is Rh positive. They have this particular factor in the blood. When the factor is not present, then we refer to the individual as being Rh negative.

Mr. FLOOD. Suppose you have a Negro patient, what do you do about that?

Dr. LAVECK. In the Negro about 92 percent are Rh positive.

Mr. FLOOD. Is that good?

Dr. LAVECK. For this purpose, that is good. In orientals, almost all are Rh positive.

### RESPIRATORY DISTRESS SYNDROME

The newborn infant faces certain very specific hazards during his first days of life. The respiratory system must make the greatest degree of adjustment in adapting to life after birth. Approximately 20,000 newborn infants die each year from the respiratory distress syndrome. We do not know the cause of this disease. So far, no specific method of treating this disorder has proved to be reliable. Therefore, more research will be conducted and new treatment methods will be explored.

Mr. FLOOD. What is that?

Dr. LAVECK. The respiratory distress syndrome is a particular type of respiratory problem seen primarily in premature infants in which a membrane is formed in the air sacs of the lung that prevents expansion of the lungs and normal ventilation of air.

Mr. FLOOD. What is a premature infant?

Dr. LAVECK. By definition, a premature infant is one born alive after less than 37 weeks gestation. In the past we referred to prematurity in terms of an infant weighing less than five and a half pounds at birth.

Mr. FLOOD. What would be the normal gestation period in weeks?

Dr. LAVECK. Between 38 and 40.

Mr. FLOOD. This is 37?

Dr. LAVECK. That is right.

Mr. FLOOD. This is pretty close, isn't it?

Dr. LAVECK. This is true, and the closer the pregnancy gets to term the better is the chance for infant survival.

MENTAL RETARDATION

Not all infants with significant health problems die.
Some, though surviving, develop handicapping disabilities. Mental retardation often stems from an abnormality originating during pregnancy, at birth, or shortly after birth. It can also be caused by lack of appropriate stimulation at given periods of development. Over 100,000 infants born each year are destined to manifest evidence of mental subnormality later in life. During the past 3 years, 12 institutions have received awards from the National Institutes of Health for the construction of mental retardation research centers.

MONGOLOID CHILDREN

Mr. FLOOD. The committee had an inquiry from a distinguished American who is concerned about this problem of mongolism. This is a pretty advanced condition of retardation, is it not?

Dr. LAVECK. It is generally associated with severe to moderate mental retardation.

Mr. FLOOD. Isn't it severe only?

Dr. LAVECK. No. The term "mongoloid idiot" is a misnomer in that profound retardation is not generally the rule.

Mr. FLOOD. What does the term "mongoloid" mean?

Dr. LAVECK. A mongoloid child is one who has a congenital defect due to the presence of an extra chromosome.

Mr. FLOOD. What does that mean, Doctor?

Dr. LAVECK. Chromosomes are the linear, threadlike bodies that are present in all living cells and carry genetic information.

Mr. FLOOD. Why would this happen to this mongoloid?

Dr. LAVECK. There are two primary mechanisms that result in the mongoloid child having 47 chromosomes or the equivalent chromosome complement rather than the normal number of 46.

Mr. FLOOD. Why?

Dr. LAVECK. One is due to a rather complex process called "nondisjunction." This simply means that when the ovum is being formed the chromosomes do not separate appropriately during the reduction division stages and the mother's egg contains one more chromosome than normal.

That is just one mechanism. There is also a hereditary mechanism by which mongolism can be perpetuated in families due to another complex genetic mechanism called translocation.

Mr. FLOOD. This is not necessarily hereditary, is it?

Dr. LAVECK. The translocation type can be inherited. This makes up about 5 percent of all mongoloid births.

Mr. FLOOD. How many are there?

Dr. LAVECK. One out of every 700 newborn infants will be mongoloid.

Mr. FLOOD. Is that bad?

Dr. LAVECK. That is bad.

These construction funds were made available through Public Law 88–164. The research and research training in these centers promises to make a significant contribution in our efforts to prevent, diagnose, and manage mental retardation.

FAMILY PLANNING

The Institute is convinced that family planning services are effective measures to reduce both infant mortality and mental retardation. Mongolism, or Down's syndrome, is a good example of this point. Approximately one out of every 700 newborn infants has mongolism. For women who bear a child after they are 45 years old, however, the risk of having a mongoloid child is about one chance in 40. If family planning information and services were made available to older women, mongolism and other congenital malformations would be reduced.

Mr. FLOOD. How would more family planning information and services be made available?

Dr. LAVECK. This is not the responsibility of our institute, of course, but the Public Health Service, the Office of Economic Opportunity and the Children's Bureau are at the present time enlarging and expanding their programs to make these services available to women who generally do not have access to these services.

CONTRACEPTIVE METHODS

We support research in reproductive biology, contraceptive methods, and social aspects of family planning. The Institute is aware that an array of contraceptive methods must be developed if the diverse needs of all populations are to be met.

Mr. FLOOD. What do you mean by "array?"

Dr. LAVECK. We mean although the oral contraceptives and intrauterine devices are effective contraceptive techniques, we need additional contraceptive methods because for various reasons present methods may not be acceptable to all people.

Mr. FLOOD. What is your opinion about the much-publicized pill? What is "the pill," by the way?

Dr. LAVECK. "The pill" is a combination of two hormones, an estrogen and a progestogen. This is a highly effective method of regulating family size.

Mr. FLOOD. Would you prescribe them?

Dr. LAVECK. Yes, I would.

Dr. SHANNON. Mr. Chairman, I think at this point it might be wise to realize that while one talks of "the pill"——

Mr. FLOOD. What is "the pill"?

Dr. SHANNON. There are a variety of pills that alone or in combination affect the estrous cycle and ovulation. There are a number of these substances, some of which interrupt the estrous cycle; others of which, at substantially lower doses, would appear to prevent fertilization without at the same time inhibiting ovulation or being associated with very striking, general bodily changes.

The thing that precipitates this interruption on my part is that the news media talk about "the pill"—and they have been talking about "the pill" now for 4 years—as though this were a technique or a device that was discovered some 4 or 5 years ago and that has remained constant. There is an extraordinarily active area of investigation that we feel warrants very thorough exploitation.

Mr. FLOOD. Would you prescribe it, "the pill"?

Dr. SHANNON. As I say, there is no such thing as "the pill".

I would be willing to prescribe——

Mr. FLOOD. "A pill?"

Dr. SHANNON. In terms of my understanding of ordinary morals and the ethics of the religion to which I belong——

Mr. FLOOD. But there is no such thing, despite the news media, as "the pill"?

Dr. SHANNON. There is no such thing as the "the pill", no, sir.

Mr. FLOOD. Do you agree, Doctor?

Dr. LAVECK. There are numerous preparations.

Mr. FLOOD. For the purpose of emphasis, I repeat, there is no such thing as "the pill".

Dr. LAVECK. That is correct.

Mr. FLOOD. I wonder why we don't make a point of that?

Dr. SHANNON. This is why I interrupted the record, sir.

Dr. LAVECK. However, new methods should be based on a better understanding of reproductive biology. After a sound scientific base has evolved, we will direct our efforts toward the development of new contraceptive techniques.

GERONTOLOGY RESEARCH CENTER

At the other end of the lifespan, the Institute is proud to report that the new Gerontology Research Center Building, located at Baltimore City Hospitals, has been completed, and is in use. When fully staffed, the new facility will provide space for approximately 400 research workers. It is the largest center for gerontological research in the world, and will provide regional, national, and international stimulus to gerontological research.

Mr. FLOOD. Why is it at Baltimore?

Dr. LAVECK. This has a long history, Mr. Chairman. In about 1941 the Public Health Service developed a small research unit dealing with aging and located it at that time at the Baltimore City Hospitals.

Dr. SHANNON. Mr. Chairman, when this activity was started, we did not have access to human study material. It was associated with the Baltimore City Hospital so that individuals in the older age group could be studied as such.

NIH is in a suburban location and did not have access to normal aged population groups in such things as rest homes or homes run by societies, or indeed, population groups that were cared for by welfare departments.

The medical and welfare system of Baltimore made this a natural place to go to be able to follow, over long periods of time, groups of older people.

The program, as it developed in the forties and the fifties, became so tightly integrated with the activities of the Johns-Hopkins Hospital and the medical school, with the University of Maryland and its medical school, and with the Baltimore City Hospitals themselves, that it was logical to leave it there and provide them with resources for such a program rather than attempt to move it to Bethesda at the time the Clinical Center was built.

Dr. LaVeck. The opening of this new facility will permit the expansion of the longitudinal studies. These have been underway for nearly a decade, and have already resulted in findings indicating that decline in function with age is quite complex, and more subtle than was previously believed. The new facility will also permit the expansion of the Center's other programs of research related to alterations occurring in the human being during the aging process.

BEHAVIORAL SCIENCES

Mr. Chairman, the Institute is convinced that the behavioral sciences have much to contribute to our Nation's health. Thus our programs reflect the need to understand the particularly important behavioral events of both ends of the life spectrum, and the interpersonal, familial and societal circumstances that affect the developmental process in both the normal and abnormal individual.

NATIONAL FERTILITY STUDY

In the past year this conviction has proved productive. The national fertility study, supported by us, indicates that expectations of family size, for most American couples, remain much as they were in 1955. Through research at the University of Minnesota we have learned that children from lower class families have positive attitudes toward schooling, but, like their middle-class peers, grow more negative as their school experience progresses.

Mr. Flood. Why did you select the University of Minnesota?

Dr. LaVeck. This is the area in which the particular study was conducted. The proposal was presented by an investigator at the university.

MENTAL RETARDATION COUNSELING

We have learned, through a study in the Institute's Children's Diagnostic and Study Branch, that parents of mentally retarded children gain much from appropriate counseling concerning their children's handicaps.

Mr. Flood. At what level?

Dr. LaVeck. This was a study conducted at the National Naval Medical Center in Bethesda. Some 40 families were evaluated.

Mr. Flood. How do they get into the Naval Medical Center?

Dr. LaVeck. These are children referred to our unit from the Naval Hospital. They are all dependents of military personnel. These families were interviewed before and after a multidisciplinary evaluation of their children's capabilities and deficiencies.

Mr. Flood. This is a big cross section, do you think?

Dr. LaVeck. No, I don't think this is a good cross section of mental retardation in general.

Mr. Flood. It is better than nothing, you say?

Dr. LaVeck. There are many benefits from this type of arrangement but we don't see children who represent all socioeconomic groups. Our investigators concluded that after counseling, the parents were more realistic in regard to their children's capabilities.

Mr. Flood. How do you counsel somebody like that? Is this the mother?

Dr. LaVeck. We generally see both the mother and the father. The counseling is carried out by the staff.

Mr. Flood. Here is a building and here is a door and they walk in. What happens?

Dr. LaVeck. Even before they walk in, we have screened these children and their families to make certain that they are of interest to us from a research standpoint and have made a home visit to assess the situation at home. After they walk in the building, they are seen by a social worker, psychologist, pediatrician, neurologist, speech and hearing consultant and various other professional people.

Mr. Flood. Do they cooperate when you get that far?

Dr. LaVeck. We have had excellent cooperation, yes.

Dr. Shannon. Of course, the advantage is that they are related to the naval establishment. They are acquainted with naval processing from the standpoint of medical care programs and, importantly, it is easy to follow these people over long periods of time.

Mr. Flood. They are acquainted with discipline?

Dr. Shannon. Yes, sir.

Mr. Flood. How about people who are not so acquainted?

Dr. Shannon. This is one of the reasons Dr. LaVeck said this is not truly a representative sample. But it is our belief, at this time, that this represents such a unique opportunity to see a segment of mental retardation in a specific environment and to find out certain things about this highly controlled segment which then can be applied to broader population groups.

Mr. Flood. Most people are scared to death of you highly trained professional fellows, beginning with me. When they walk into a building, I just wonder.

Dr. Shannon. They are used to going to that building for medical care in general, so it is very helpful.

Dr. LaVeck. We have also learned that good housing has a beneficial effect upon the social and psychological adjustment of older people.

The Institute's interest in the interface between the behavioral and biological sciences is nowhere more clearly demonstrated than in its research on the relationship between nutrition and intellectual development. Because of recent findings concerning the effects of diet on the development of intellectual capacity, the Institute is supporting a long-term study to determine what effect improved nutrition has on growth and development.

Mr. Chairman, in the 5 years since the Institute was established, and in the years to come, it has and it will make every effort to acquire new knowledge concerning developmental processes which, when applied, will improve the health of all our citizens, and the quality and vigor of their lives.

### SUMMARY OF 1969 BUDGET REQUEST

For our activities in the coming fiscal year, we are submitting a request for $75,394,000. This, compared with an operating level of $68,035,000 for 1968, represents an increase of $7,359,000. Of this sum, we are requesting $2,159,000 for grants, of which $1,818,000 is for research and $341,000 is for fellowships and training. For direct

operations, which include collaborative research and development, we are requesting an additional $5,200,000.

I shall be happy to answer any questions.

COLLABORATIVE RESEARCH AND DEVELOPMENT

Mr. FLOOD. Half of the total increase is for "Collaborative research and development," which will more than treble the dollar size of your program. Have you read the newspapers with regard to this 1969 budget? Of course, you prepared this budget back in October or November.

Dr. LAVECK. In that time range.

Mr. FLOOD. Tell us what is involved that requires this great emphasis on one program?

Dr. LAVECK. For collaborative research we are giving emphasis to population studies, but our total requested increases focus on three areas; mental retardation, population research, and aging. These are three areas we are emphasizing in this budget submission. I would be happy to go through these three areas if you would like me to do so.

GROWTH OF APPROPRIATIONS FOR INSTITUTE

Dr. SHANNON. You have to realize this is the newest of our categorical institutes. The first year was spent in pulling together those elements of the program contained in other institutes that could be most profitably grouped here.

The second and third years represented growth of some programs and the Institute's budget actually went from $55 million in 1966 to $65 million in 1967. This $10 million increase reflected the newness of the Institute and the absolute essentiality of certain elements of a new program.

Mr. FLOOD. Why the emphasis on this Institute?

Dr. LAVECK. We have a very broad mission, Mr. Flood.

Mr. FLOOD. How about general medical science? Don't they have a broad mission, these general medical people who just left the witness chair?

Dr. LAVECK. I am sure they do but the attention that needs to be given to mental retardation, population control, and aging is so great that we feel efforts have to be made to move these fields in a positive way.

MENTAL RETARDATION

Mr. FLOOD. Do you find a very wide, general acceptance of this attack on mental retardation as opposed to your mother's time?

Dr. LAVECK. I think in general we have had support from universities.

Mr. FLOOD. The general public?

Dr. LAVECK. From the general public unquestionably, yes, we have had good support.

Dr. SHANNON. This results from people being willing to speak about it. A similar situation obtained in mental health in the fifties. Prior to that time these people were put in the backroom and not spoken about. It was a disgrace.

Mr. FLOOD. He was put in the attic and tied to the end of an iron bed with a chain?

Dr. SHANNON. No attempt was made to integrate them into the family or community life.

Mr. FLOOD. Your best analogy is the attitude toward venereal disease, which is now out in the open.

Dr. SHANNON. Yes. A very good parallel.

CONTRACEPTIVES

Mr. FLOOD. You are putting a lot of emphasis on your work on the safety of contraceptives. Food and Drug had a great deal to do with this by law.

You are working on the development of new contraceptives. I am sure all the large drug houses are doing the same thing.

Dr. LAVECK. Our emphasis is actually on the mechanism of action of contraceptives, the medical effects of contraceptive agents, and the development of new ones.

Mr. FLOOD. The point I was going to make was there seems to be a matter of duplication; a little duplication is a good thing. But I repeat again for the purposes of emphasis. This budget for this year is such that it is questionable whether we can presently afford it. I don't question whether it is good or bad. Can we afford it?

HIGH PRIORITY GIVEN INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Dr. SHANNON. May I answer that question in a little different way? Given some cuts, if this comes about, if we are given the freedom to distribute those cuts, if we can maintain in this appropriation at the very least its current activity, even though it meant cutting back in some of the other appropriations——

Mr. FLOOD. Doesn't it occur to you this would be vulnerable on the public square?

Dr. SHANNON. I don't believe so, sir. This gets at the heart of obtaining an understanding of some of our really great social problems of today. That is, what are the factors——

Mr. FLOOD. Yes, but I mean "now," when our economy is in great difficulty.

Dr. SHANNON. Given cuts to distribute, we would protect this appropriation to a substantially greater degree than some of the other appropriations. This would be on the basis of our best professional opinion.

Mr. FLOOD. Are you talking about priorities?

Dr. SHANNON. Yes, sir. We would give this very high priority.

Mr. FLOOD. This is of high priority.

Dr. SHANNON. I think they are all high priority, but among the high priorities—as one might say, some are more equal than others.

Mr. FLOOD. "Now?"

Dr. SHANNON. "Now," yes, sir.

I think all of the programs that are aimed at salvaging young children are at a tremendous disadvantage and will continue to be at a disadvantage until more knowledge is available concerning the bio-

logical, the emotional and intellectual development of the child. I think that all of our programs that relate to the elder citizen are at a disadvantage until more information is available on the biological, emotional, and intellectual deterioration that occurs in the older citizen. So we would give extraordinarily high priority to these programs, given a requirement to distribute any restriction on funds across all of the Institute activities, sir.

LABORATORY AND CLINICAL RESEARCH

Mr. FLOOD. The only other increase of any consequence that you have is $550,000 and 83 jobs in laboratory and clinical research.

What activities do you have planned for this increase and tell me how to counter the statement?

Certainly this is important, but we can better afford to postpone it a while than we can afford to increase the appropriation under current fiscal circumstances.

This is the kind of argument I am going to be faced with. How would you answer it?

Dr. LAVECK.My reply is that our intramural program got underway in 1965. We have recruited some outstanding investigators who will be pursuing studies germane to the mission of our Institute. We have been waiting for facilities to be constructed and renovated. These are now going to be made available to us. I might use the Gerontology Research Center as a good example. This is a facility that will accommodate 300 staff members.

Mr. FLOOD. This is bricks and mortar, a building?

Dr. LAVECK. This is a building. By the end of this year we will have 130 people on board. We are asking for 40 positions and $265,000 to increase that staff to 170. We are not going to be at capacity next year. We will be at about 55 percent of capacity. We would not request funds to permit us to completely staff such a facility with the fiscal situation being what it is. We know how difficult it is to recruit people and programs must be developed in an orderly way; however, the opportunity now exists to move into the new facility and expand and continue some of the studies that have been done in a very crowded situation at the Baltimore City hospitals.

Mr. FLOOD. I quoted to you what somebody will likely say to me when we come to mark up this bill. I have no quarrel with your premise, but can we afford it now? This man has no quarrel with what you want to do, but can this be postponed a while? A year? One year?

Dr. LAVECK. I think it would be difficult to completely limit the growth of that program.

MENTAL RETARDATION RESEARCH CENTERS

Mr. FLOOD. In research grants, you have a net minus of $182,000 for all activities except for the mental retardation research centers where you are requesting an increase of $2 million.

Dr. LAVECK. That is correct.

Mr. FLOOD. Describe such a center and tell us about this. How would you pick a center? Where is it located? How would you use this $2 million?

Dr. LaVeck. As I mentioned in my opening remarks, there are 12 centers that are now being constructed.

Dr. Shannon. These centers were authorized in the Mental Retardation Facilities and Community Mental Health Centers Construction Act of 1963. They were limited to, I believe, $26 million for the construction of approximately this number of research centers. It was, at that time, felt that the disciplines that found no representation is the structure of graduate biological divisions of the universities, or in the medical schools, would have to develop a new approach to the important problems in this area. It was felt that they could not be grafted upon the departmental structure of institutions of higher education, but would require an integrated approach that really required wholly new resources of a type not generally available.

### LOCATION OF MENTAL RETARDATION RESEARCH CENTERS

Mr. Shriver. Could you tell us where these places are?

Dr. LaVeck. Yes. The 12 centers are located at the University of Chicago; Albert Einstein College of Medicine in New York City; the University of Washington in Seattle; Children's Hospital in Cincinnati; the George Peabody College for Teachers in Nashville, Tenn.; the University of Colorado Medical Center; the University of California at Los Angeles; the University of Kansas; the University of North Carolina; Walter E. Fernald State School in Waltham, Mass.; the Children's Hospital Medical Center in Boston; and the University of Wisconsin; a total of 12. Eight of these will become operational by the end of fiscal year 1969.

Mr. Shriver. How are you going to use the $2 million? Perhaps you will cut back these other things, but there are 2 million fresh dollars.

Dr. LaVeck. It is estimated by the directors of these centers, after very careful scrutiny of their plans, that 2 years after the centers become operational, each center will require about $2.5 million per year to carry on research and research training activities in mental retardation. This is going to be a very large program.

Mr. Flood. I know, Doctor, but we are talking about this budget—we talk 1 year at a time. We are referring to the $2 million in this budget.

Dr. LaVeck. Eight of the centers will become operational by the end of fiscal year 1969. The funds we are asking for here would be to get programs started on research in mental retardation, both the behavioral and biological aspects of this particular problem.

### FEDERAL SUPPORT FOR MENTAL RETARDATION CENTERS

Mr. Flood. What percentage will be borne by the Federal Government? Will it vary?

Dr. LaVeck. Yes; it will.

Mr. Flood. Why?

First, answer my question: What percentage is Uncle Sam paying?

Dr. LaVeck. At the present time universities indicate they will be able to support about 30 percent of the activities going on in the center and they will seek Federal support for the remaining 70 percent.

Undoubtedly our institute will be the agency most likely to be contacted for Federal support.

Mr. FLOOD. What would it cost—after they are all operating in all of these places and Uncle Sam is paying 70 percent, how much will it cost a year to run each one? Apparently there will be a variance among them.

Dr. LAVECK. The total cost for all 12 centers?

Mr. FLOOD. How much will it cost to run one, each year?

Dr. LAVECK. It will cost about $2½ million to run one center each year; 70 percent is likely to be requested of the Federal Government.

Mr. FLOOD. Every year?

Dr. LAVECK. Yes. These are estimates, of course, but the best estimates we have.

This committee last session asked us to give top priority to the development of research and research training programs in the mental retardation research centers. This is one of the reasons we have identified this for the first time as a line item in our budget so the Congress will be well aware of the magnitude of this operation.

Mr. FLOOD. Do you read the reports from this committee?

Dr. LAVECK. Yes, sir.

RESEARCH ON AGING PROCESS

Mr. FLOOD. Now what about your funds to support research in the aging process?

Dr. LAVECK. Yes.

Mr. FLOOD. The committee knows about the aging process, unfortunately, and what you have said before. Now what has happened in this field since you were here last year?

Dr. LAVECK. We have had less success in the field of aging research than in any other area.

Mr. FLOOD. Why?

Dr. LAVECK. I think there are a number of reasons. One, gerontology is a new field. The gerontologists did not form a society, even, until 20 years ago. There is no medical school that I know of that has a department of gerontology.

Mr. FLOOD. That is odd. Aging is not very new, is it?

Dr. LAVECK. The study of aging is.

The quantity of research requests we get is very small. Out of 11,000 applications submitted to NIH in 1967, just 59 dealt with the aging process. I would say that the quality of applications is perhaps somewhat lower than those for other areas within our Institute.

In order to give this field the push and thrust that it needs, we have focused on two approaches. One is to increase training, and we will spend well over $2 million to train people in the field.

Mr. FLOOD. What percentage of your funds do you dedicate to examination of the aging process?

Dr. LAVECK. We will spend approximately $8.2 million in fiscal year 1969.

Mr. FLOOD. What is the percentage?

Dr. LAVECK. 12.3 percent of our total budget.

Mr. FLOOD. Is that good? Is that enough? Is that too much? Why not 5 percent, or why not 30 percent? Why 12.3 percent?

Dr. LaVeck. I personally feel that we should be spending more in this area, particularly in our intramural program at the Gerontology Research Center, where we have an excellent opportunity to give a national and international thrust to this particular field.

Mr. Flood. Mr. Laird——

Mr. Laird. I have no questions.

Mr. Flood. Mr. Natcher?

Mr. Natcher. No questions, Mr. Chairman.

Mr. Flood. Mr. Shriver?

MENTAL RETARDATION CENTERS

Mr. Shriver. I wanted to pursue your discussion about those institutions dealing with mental retardation. You mentioned Kansas among them.

I received a letter the other day. I haven't been able to find out what the man is talking about. He is talking about a program which revolves around our Parsons, Kans., center.

Dr. LaVeck. The Parsons State Hospital and Training Center has new construction going on for this particular program, yes.

Mr. Shriver. He mentioned to me that the State Legislature of Kansas has already appropriated $1 million for it.

Dr. LaVeck. The research centers in Kansas will be partially completed by July 1969. There are three units associated with the University of Kansas: One at the medical school, one at the university in Lawrence, and the other at the Parsons center. Two of these are scheduled to be completed during fiscal year 1969. The Parsons unit will be completed in August 1969.

Mr. Shriver. Has this been cut back by the Budget Bureau prior to coming here?

Dr. LaVeck. The support?

Mr. Shriver. For these three research centers?

Dr. Shannon. There was a cutback, Mr. Shriver.

Mr. Shriver. Where?

Dr. Shannon. In the first place, we cut back the allocation of funds available for us to distribute, though we gave it high priority among the activities that we were considering. Then there was a further cutback up the line.

STUDY OF ESKIMO WOMEN

Mr. Laird. I had one item that concerned me a little, on page 67 of your justification. It is an item that could very well be referred to on the floor because of the manner in which it is presented in the justifications. If you will look on page 67, you refer to a study of the "Menstrual Cycles and Pregnancies of Eskimo Women."

For the record, I'd like to know how much is this project going to cost and what valuable information do you expect to gain? We may be asked about this on the floor, because you put this out as an example of your grant projects, but you give no explanation of what the purpose is and what knowledge we might gain from this grant.

Dr. LaVeck. Our major effort has been in a large group of women in Minnesota who have been followed since 1934, but for comparison purposes we felt that it would be of value to pursue this type of study

in Eskimo women to see how their menstrual cycles compared with those in the State of Minnesota.

Mr. LAIRD. I suggest you extend your remarks on this subject.

Dr. LAVECK. Very well.

(The information requested follows:)

THE STUDY OF THE MENSTRUAL CYCLE OF ESKIMO WOMEN

The study of the menstrual cycle of Eskimo women is a reimbursable agreement with the Arctic Health Research Laboratory of the Public Health Service, estimated to cost $36,000 in fiscal year 1969. This study has been undertaken to expand the knowledge and test the findings of a comprehensive study of the human menstrual cycle which has been continued since 1934 in other parts of the United States.

In this longitudinal study, great variation in the characteristics of the human menstrual cycle has now been demonstrated and quantitatively defined. It is clear that each woman has her own periodicity in this function, that 28 days is just a statistical average, and that complete regularity in rhythm does not exist except over very short intervals of time. Racial differentiation has been proven as a factor affecting the duration of pregnancy. This fact has increased speculation among students of fertility that the environmental factors associated with altitude, with length of day (a factor known to influence reproductive cycling in lower forms of life), and with the cultural factors of modern civilization, affect the basic biology of human reproductive functions.

Extension of our studies to include the Eskimo provides a unique opportunity to test these postulates under excellent circumstances for a very different ethnic group. Public health nurses working in the Eskimo villages with particular health research projects, such as prophylactic agents for the reduction of ear infections, have asked the Eskimo women if they would care to participate in the menstrual history project also. The response has been remarkable—100 percent completely voluntary enrollment of all women and girls in the villages being visited in the Bethel area and at Point Barrow. As a control, well over 200 teachers in the Anchorage school system and their friends are likewise keeping the records as very interested volunteers. This menstruation and reproduction study has been spontaneously welcomed by women wherever it has been extended, and we are most hopeful that its definitive results will prove of great value in current attempts to control the "population explosion."

STUDY OF FAMILY PLANNING

Mr. SHRIVER. You are requesting five positions and $3.5 million for collaborative research, a part of which will be used to study the psychological aspects of family planning. What do you mean by that? What is that study going to be?

Dr. LAVECK. We know very little about why families do or do not use contraceptive methods. We know practically nothing on what effect contraception may have on premarital sexual behavior, on venereal disease, or on family stability. We do not know why some people avail themselves of family planning services and others do not. This is the type of information we are seeking.

Mr. SHRIVER. I am on another subcommittee that has to do with foreign aid expenses. Last year we appropriated, I think, $20 million for family planning in programs overseas, in many countries. Do we know enough about it to be spending that kind of money in foreign countries?

Dr. LAVECK. I think there would be much to be learned by studying the social aspects of family planning in foreign countries as well as in this country so that one can best utilize the results to develop effective family planning services.

Mr. SHRIVER. I am talking about actual money to be used in a program of cutting down on the rates of birth.

Dr. LaVeck. We have met with the people from AID on a number of occasions, and I think there is enough information that warrants a strong program in India and some of the other developing nations.

Mr. Shriver. Thank you.

Mr. Flood. Mr. Smith?

COORDINATION WITH OTHER NIH PROGRAMS

Mr. Smith. In the National Institute of Neurological Diseases and Blindness they have 1,612 regular research projects and in the justification it says:

> The majority of them were fundamental studies, however, not only on the causes, treatment, and prevention of all the health problems mentioned below but on the very mechanisms by which cells, genes, viruses, proteins, molecules, and other basic biological entities reproduce and function.

That is the same area you are workin in; is it not?

Dr. LaVeck. We do support work in those fields as it relates to our five major areas of interest: population, infant mortality, growth and development, aging and mental retardation.

Mr. Smith. To what extent is there overlapping and how do you coordinate so there is no waste in both of you working on the same kinds of projects?

Dr. LaVeck. We certainly have a very close working relationship with the National Institute of Neurological Diseases and Blindness.

In the area of mental retardation, for example, we have met periodically for several years, looking at possible duplications of effort, or gap areas and, in general, our approach is sufficiently different that we do not encounter major duplication of effort.

Dr. Shannon. Could I give you a very good example of gross apparent duplication: The major thrust of the perinatal study Dr. Masland discussed before this committee is to determine the causes during pregnancy of mental retardation. The primary cause at the time that study was developed related to brain damage. This was started in the fifties long before we had a Child Health Institute and it was left in the Neurological Institute because they had the management devices and the program was already set up there. But this has very broad implications for many things that Dr. LaVeck is doing in mental retardation.

Indeed, these two institutes share the Puerto Rican facility, the primate facility in Puerto Rico, in the exploration of some of these phenomena.

This is an example of an area in which two institutes are profoundly interested where, I would say, that if there was not some overlap, there would be broad deficiencies in program development.

Now, a mechanism that permits an assessment of overlap and its prevention is that we have central receipt of all research grant applications at one point. Assignment to this Institute or the other is under specific and rigid guidelines, and there is central analysis of the aggregate activities.

Mr. Smith. Advisory committees for each institute will not have before them what the other one has.

Dr. Shannon. No, sir, but they will have knowledge of the activity in the related area.

Mr. FLOOD. You have an advisory committee for each institute in your shop?

Dr. SHANNON. Yes, sir, but we have central receipt of all research grant applications. We have allocation according to rigid guidelines and then analysis of our research program, in part in relation to specific institutes and in part in relation to aggregate activity. We are as much concerned with deficiencies in program as in overlap.

Mr. SMITH. The biology program in both of these institutes overlap.

Dr. SHANNON. You see, there is a great deal of overlap because the categorical nature of our programs is such that it is difficult, if not impossible, to get total separation, so certain arbitrary separations are made. This was the reason, really, for the creation of the National Institute of General Medical Sciences. It became apparent that certain discipline-oriented studies in genetics, biochemistry and the like had direct relevance to the activities of a number of institutes.

It seemed wiser, therefore, to localize these within a single organization, and more particularly in terms of training. The bulk of our predoctoral training supported is provided by the National Institute of General Medical Sciences. Many of the people who are trained at the predoctoral level will eventually find their way into the programs of heart, cancer, child health, or what not. But it seemed not very sensible to carry predoctoral education in each of the several institutes. It made management difficult, it made analysis very difficult and, in general, the ultimate area that the scientist is going to work in is not totally determinable at the predoctoral level. So this was one of the reasons for centralization of that function.

### DIETARY STUDIES

Mr. SMITH. You said you are going to conduct some studies on the effect of diet. How do you do that? Would some children be starved and some others fed all the protein they want or how do you do that?

Dr. LAVECK. No, sir. We have a project, which is now in its third year, being conducted in Guatemala. There are some six villages in the highlands of Guatemala which are really impoverished areas. The study will entail giving children and pregnant women in three villages, in addition to their regular diet, supplemental protein. The people in the other villages will receive their regular diet only and one can judge the effect of nutrition on intellectual development in this manner. Great efforts have gone into controlling all other variables that undoubtedly relate to intellectual deficit, such as social factors.

Mr. SMITH. Are you dealing with protein only or will you also consider the intake of carbohydrates?

Dr. LAVECK. Protein and vitamins are the major supplements, although we also have to improve caloric intake. The animal work done in this area indicates a protein deficiency is the particular nutrient that may lead to deficits in intellectual development.

Mr. SMITH. What form of proteins?

Dr. LAVECK. The protein we are giving is provided in a product called Incaparina. This is a milk, soybean and corn mixture.

Mr. SMITH. Do you feel it does not really make much differences whether it is in the form of animal protiens such as meat or cheese rather than vegetables protiens, in this mixture? Does that make any difference?

Dr. LAVECK. Proteins are made up of amino acids. To my knowledge there is no evidence that one form of protein might in some way be superior to another as long as the protein provides the proper mixture of amino acids.

Mr. SMITH. Have you experimented with that or do you think it is not necessary? Are you so sure that it is not necessary?

Dr. LAVECK. I am only generally familiar with the field of nutrition. Such work has been done in the past. In particular, Incaparina has been studied extensively and has been judged a good form of protein.

Dr. SHANNON. Mr. Smith, the biological value of a protein depends upon its specific amino acid content. In developing countries where cereal grains are the primary source of calories, the protein content is low but more importantly the lysine content of the protein is particularly low. So you deal with the total protein contained in the cereal grain and, in addition, the specific mix of amino acids. All nutritional experiments on the human have demonstrated that the amino acid content, or the amino acids available, determined the biological net worth of the protein, rather than its source.

GUATEMALA EXPERIMENT

Mr. SMITH. I was really driving toward another question, and that is regarding the experiment in Guatemala. Wouldn't you probably have a different result from increasing protein where the carbohydrate intake is at a different level than where it is more normal?

Mr. FLOOD. That is an excellent question.

Dr. LAVECK. During the past 3 years, surveys have been carried out in these populations in Guatemala to determine the precise diet that is being used by the people at the present time.

Mr. SMITH. Is their caloric intake much different than in the United States.

Dr. LAVECK. The deficiency you were talking about is one of calories rather than of carbohydrates. Calories come from fat and protein as well as from carbohydrates.

In Guatemala, the total caloric intake certainly is less than in the United States. There is no question about that. But their diet contains a relatively higher carbohydrate content.

Mr. SMITH. If the calories are less, whatever the form of ingredients, would you have a different result in increasing protein there than you would with the average caloric intake in the United States? In other words, how accurate—how good will this study be if it is performed in a country where the total caloric intake on the average is much less than it is in the United States.

Dr. LAVECK. Your question is, Can this be applied to problems in this country?

Mr. SMITH. Well, to the full extent.

Dr. LAVECK. There is certainly a great difference in the degree of malnutrition we see in Guatemala as compared with this country. The purpose of the study in Guatemala is to determine, not only if poor nutrition has a detrimental effect on intellectual development but if so, is it reversible and when is it reversible? If the poorly nourished person in Guatemala does not show defects in intellectual development, then we would not expect to find effects in the United States. If effects are seen, we will obtain important information on when supplementation should be undertaken. For instance, if a pregnant woman receives a poor diet and the child receives a poor diet, will supplementation later in childhood reverse the adverse effects of prenatal malnutrition? This is one of the questions we hope to answer.

Mr. SMITH. This is really a very limited experience with diet.

Dr. LAVECK. It is a study in seriously impoverished areas with nutritional deficits much greater than one would encounter in this country.

Mr. SMITH. We see that diet can have an effect on a lot of ailments and we do not hesitate to spend several hundreds of millions of dollars to see what the drugs will do but is there any field where we are really experimenting with the effect of diet to the extent that we are with the effect of drugs?

Dr. SHANNON. I am speaking of the aggregate programs of NIH. It is certainly well appreciated that—certainly in developing countries but, we feel, probably also in certain areas in this country—that child development is seriously impaired by inadequacy of diet.

Now the studies that are undertaken by us are not large in proportion to the problem.

Historically, after very extensive expenditures in this country on caloric intake and its needs and protein intake and its needs, the science of nutrition appeared to have little to offer in terms of advances. Substantial work that had been going on in the 1930's and 1940's and early 1950's was practically deemphasized.

We became involved with developing countries through AID programs and it became clearly apparent, there, that although caloric intake was low, the specific efficiency that was of overriding importance in the developing countries was protein deficiency. It was possible to show, in these developing countries, that simple supplementation by protein was adequate to reverse these very serious processes.

Now the importance of total caloric intake stems from the fact—and it is an established fact—that if total caloric intake is below body requirements, then the proteins—the amino acids contained in the protein—will be utilized for energy rather than for the synthesis of body protein which is required for growth and development.

In the studies that are going on—Guatemala is mentioned, and there are some of a somewhat similar nature planned in some villages north of Bangkok, in Thailand—an estimation has been made that it is possible to hold total calories constant and make this up by a protein supplement in a rigidly controlled study and then measure the influence of this on intellectual development. But it is more complicated

than that because in these situations—whether it be in Guatemala, or some of the areas that have been pointed out in our own country that are presumed to be deficient—there is the additional fact of infection, or parasitic infestation. This, in turn, leads to anemias and greater susceptibility to disease.

So that in the study in Thailand, for example, in association with the Rockefeller Foundation, we are establishing in these villages a clinical research unit that will be associated with the developing medical school at Chengmai, where samples of the population groups can be brought in and studied in detail relative to metabolic phenomena.

It is not convenient to do that kind of detailed study in large population groups in Guatemala. On the other hand, the activities in Guatemala are integrated with the activities of INCAP. INCAP is a Central American collaborative effort by Costa Rica, Guatemala, Panama, El Salvador, Honduras, and Nicaragua, who set up a laboratory to explore how, within native means, it is possible to improve the quality of cereal grains and other sources of calories to the nutritional advantage of these population groups. The study that Dr. LaVeck mentioned should therefore not be viewed as a study in isolation but rather as part of a very broad and very complex study in that area where many of the factors you raised are being studied by other groups in cooperation with this particular one.

### RELATIVE EMPHASIS GIVEN DIET RESEARCH

Mr. SMITH. But in the broad sense it is pretty well recognized—I assume from what I have read and heard, anyway, in the last few years—that diet does have an effect on a lot of diseases.

Dr. SHANNON. Indeed it does.

Mr. SMITH. Are we really paying enough attention to that kind of research, compared to research in drugs?

Dr. SHANNON. In the aggregate, Mr. Smith, I believe we are, at the present time, in terms of well-established diseases. In other words, a good deal of the work in the heart institutes that relates to atherosclerosis concerns itself with metabolic phenomena and the effect of diet on these phenomena.

Much of the work in other institutes have a comparable relationship.

Our belief that we knew too little about this in the United States led the Surgeon General to set up, in the Bureau of Disease Prevention and Environmental Control, a nutrition unit that will have responsibility for doing some of the detailed surveys, such as we have done in developing countries, on some of the isolated population groups in this country, in order to determine whether, indeed, we can uncover the deficiencies of which you speak that may underlay some of the problems, for example, of high perinatal deaths, high infant mortality, things of that general sort, that are not discoverable unless one has definitive nutritional data on the basic population group in which these things occur.

Mr. SMITH. Is any research being done on the effect of diet upon eyesight?

Dr. SHANNON. Yes; that is being done in some of the international programs——

Mr. SMITH. Not at the National Institutes of Health?

Dr. SHANNON. Not at the NIH. There was an international activity—that, interestingly enough, was supported largely by ARPA as part of the international nutritional activities—that developed information to indicate the profound influence of certain vitamin shortages on the ability of whole population groups to develop and maintain normal sight.

I have in mind, particularly, a survey they made in Taiwan where remedial action in relation to vitamin supplements completely eliminated this disorder. Vitamin A is particularly involved here because vitamin A becomes a part of the optical apparatus. It provides sensitivity of nerve cells to light. There are some other vitamins that have a less direct influence.

I think these are well known in terms of the ability of specific vitamins to affect sight.

What is not known in this country is the extent to which special deprived population groups have this as a normal habit of life and thereby are placed in difficult positions to develop.

Mr. SMITH. I wonder how much you really want to stand on the assertion or conclusion that protein is protein? Chicken feathers are 90 percent protein but you would not include that in this experiment, would you? Intestinal wastes are very high in protein but you would not want to use that in the experiment. There must be some difference in the form of protein; isn't there?

Dr. SHANNON. Indeed there is. As I pointed out, the availability of the amino acids within the protein is the nutritional determinant rather than the source of the protein. When you say availability, if you take hair, or things like that, it is not good because the protein will not be fully digested.

If you take two types of milk protein—lactalbumin versus casein—in one the value is high and in the other it is limited. This is due directly to the amino acid content. If you take a mixture of amino acids themselves and feed them, as amino acids, instead of a whole protein and if the net content of the amino acid mixture is identical with the amino acid content of a digestible protein, the biological effect will be the same.

Mr. SMITH. In all these respects do you consider what you are using to be foods that we use commonly in the United States?

Dr. LAVECK. Yes.

Mr. SMITH. You are not using any whole fishmeal in that project; are you?

Dr. LAVECK. No.

Mr. FLOOD. Mr. Hull?

Mr. HULL. No questions, Mr. Chairman.

JUSTIFICATION MATERIAL

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

National Institute of Child Health and Human Development

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $68,621,000 | $75,394,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 47 | Research | | $42,447,000 | | $44,265,000 | | $+1,818,000 |
| | General research support grants | | (4,264,000) | | (4,082,000) | | (-182,000) |
| | Scientific Evaluation | | (100,000) | | (100,000) | | (0) |
| | Categorical clinical research centers | | (500,000) | | (500,000) | | (0) |
| | Mental Retardation Centers | | (0) | | (2,000,000) | | (+2,000,000) |
| 56 | Fellowships | | 4,102,000 | | 4,193,000 | | +91,000 |
| 58 | Training | | 9,762,000 | | 10,012,000 | | +250,000 |
| | Direct Operations: | | | | | | |
| 62 | Laboratory and clinical research | 271 | 5,098,000 | 354 | 6,693,000 | +83 | +1,595,000 |
| 65 | Collaborative research and development | 34 | 1,530,000 | 39 | 5,032,000 | +5 | +3,502,000 |
| 67 | Biometry, epidemiology, and field studies | 23 | 2,040,000 | 23 | 2,046,000 | ... | +6,000 |
| 69 | Training activities | 5 | 89,000 | 5 | 89,000 | ... | ... |
| 70 | Review and approval of grants | 94 | 1,954,000 | 98 | 1,986,000 | +4 | +32,000 |
| 71 | Program direction | 51 | 1,013,000 | 54 | 1,078,000 | +3 | +65,000 |
| | Total obligations | 478 | 68,035,000 | 573 | 75,394,000 | +95 | +7,359,000 |
| | Unobligated balance, reserve | 15 | 586,000 | ... | ..... | -15 | -586,000 |
| | Total obligations and reserve | 493 | 68,621,000 | 573 | 75,394,000 | +80 | +6,773,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 478 | 573 | +95 |
| Full-time equivalent of all other positions.... | 13 | 13 | ... |
| Average number of all employees..... | 407 | 521 | +114 |
| Personnel compensation: | | | |
| Permanent positions..... | $3,488,000 | $4,273,000 | $+785,000 |
| Positions other than permanent... | 99,000 | 102,000 | +3,000 |
| Other personnel compensation .... | 83,000 | 100,000 | +17.000 |
| Total personnel compensation... | 3,670,000 | 4,475,000 | +805,000 |
| Personnel benefits ..... | 401,000 | 465,000 | +64,000 |
| Travel and transportation of persons | 271,000 | 320,000 | +49,000 |
| Transportation of things ..... | 46,000 | 56,000 | +10,000 |
| Rent, communications, and utilities | 140,000 | 185,000 | +45,000 |
| Printing and reproduction..... | 86,000 | 95,000 | +9,000 |
| Other services..... | 653,000 | 700,000 | +47,000 |
| Project contracts..... | 2,957,000 | 6,349,000 | +3,392,000 |
| Payment to "National Institutes of Health management fund"..... | 2,733,000 | 3,378,000 | +645,000 |
| Supplies and materials..... | 228,000 | 252,000 | +24,000 |
| Equipment..... | 539,000 | 649,000 | +110,000 |
| Grants, subsidies, and contributions | 56,311,000 | 58,470,000 | +2,159,000 |
| Total obligations by object... | 68,035,000 | 75,394,000 | +7,359,000 |

## Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $68,621,000 |
| Unobligated balance, reserve | -586,000 |
| 1968 total estimated obligations | 68,035,000 |
| 1969 estimated obligations | 75,394,000 |
| Total change | +7,359,000 |

| Increases | Base | | Changes to Base | |
|---|---|---|---|---|
| | Positions | Amount | Positions | Amount |
| A. Built-in | | | | |
| 1. Annualization of new positions authorized in 1968 | ... | ... | ... | $395,000 |
| 2. One additional day of pay in 1969 | ... | ... | ... | 20,000 |
| 3. Annualization of the 1968 pay raise costs | ... | ... | ... | 50,000 |
| Total, built-in increases | ... | ... | ... | 465,000 |
| B. Program | | | | |
| 1. Research grants | ... | $42,447,000 | ... | 1,818,000 |
| 2. Fellowships | ... | 4,102,000 | ... | 91,000 |
| 3. Training grants | ... | 9,762,000 | ... | 250,000 |
| 4. Laboratory & clinical research | 271 | 3,433,000 | 83 | 550,000 |
| 5. Collaborative research & development | 34 | 1,463,000 | 5 | 3,500,000 |
| 6. Biometry, epidemiology, and field studies | 23 | 1,966,000 | ... | ... |
| 7. Training activities | 5 | 82,000 | ... | ... |
| 8. Review and approval | 94 | 1,313,000 | 4 | 20,000 |
| 9. Program direction | 51 | 734,000 | 3 | 20,000 |
| Total program increases | ... | ... | 95 | 6,249,000 |
| C. Centrally furnished services from the National Institutes of Health Management Fund: | | | | |
| 1. Laboratory and clinical research | ... | 1,665,000 | ... | 623,000 |
| 2. Collaborative research & development | ... | 67,000 | ... | -3,000 |
| 3. Biometry, epidemiology & field studies | ... | 74,000 | ... | 1,000 |
| 4. Training activities | ... | 7,000 | ... | ... |
| 5. Review and approval | ... | 641,000 | ... | -7,000 |
| 6. Program direction | ... | 279,000 | ... | 31,000 |
| Subtotal, management fund | ... | ... | ... | 645,000 |
| Total net changes requested | ... | ... | +95 | +7,359,000 |

Explanation of Changes

Research Grants -- The net increase of $1,818,000 results from an increase of $2,000,000 for Mental Retardation Research Centers offset by a decrease of $182,000 in General Research Support Grants.

Fellowships-- The increase of $91,000 will provide for an additional 6 fellowships.

Training Grants--The increase of $250,000 will provide for an additional 4 training grants.

Laboratory and Clinical Research--The increase of $550,000 and 83 positions will be distributed among the following laboratories and branches of the expanding Intramural Research Program: the Reproduction Research Branch will require 8 positions and $53,000 to establish an obstetrical unit to be located in a teaching hospital in the Washington metropolitan area; the Laboratory of Biomedical Sciences will need 7 positions and $46,000 to support investigations of possible permanent behavioral modifications produced by drugs and medicinals administered during embryonic and fetal development; the Behavioral Biology and Developmental Biology Branches will divide 6 positions and $40,000 to recruit branch chiefs and staffs to head these programs; the Gerontology Research Center will be assigned 40 positions and $265,000 to staff and continue equipping its new gerontological research facility; 6 positions and $40,000 will be used to recruit a clinical director and staff to direct the clinical research program; and the Office of the Associate Director will use 16 positions and $106,000 for increasing the Clinical, Research, and Staff Associates Program and to provide additional service staff for the intramural program.

Collaborative Research and Development-- The increase of 5 positions and $3,500,000 will provide for an increased research contract program in the reproduction and population and fertility control programs. There are three areas of concentration; medical effects of contraceptives, the development of new contraceptives, and the psycho-social aspects of family planning.

Review and Approval--The increase of 4 positions and $20,000 will provide for increased grants management support.

Program Direction--The increase of 3 positions and $20,000 will provide for increased administrative support.

## Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act Section 301---Research and Investigation, in general..... | Indefinite |
| Title IV, Part E--- National Institute of Child Health and Human Development..... | Indefinite |

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume IV.

The Public Health Service Act, Title IV, National Research Institutes, Part E, Institutes of Child Health and Human Development and of General Medical Sciences--

"Sec. 441. The Surgeon General is authorized, with the approval of the Secretary, to establish in the Public Health Service an institute for the conduct and support of research and training relating to maternal health, child health, and human development, including research and training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development, including prenatal development."

"Sec. 444. The Surgeon General shall, through an institute established under this part, carry out the purposes of section 301 with respect to the conduct and support of research which is the function of such institute... The Surgeon General is also authorized to provide training and instruction and establish and maintain traineeships and fellowships, in the institute established under section 441 and elsewhere in matters relating to diagnosis, prevention, and treatment of a disease or diseases or in other aspects of maternal health, child health, and human development, with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he deems necessary, and, in addition, provide for such training, instructions and traineeships and for such fellowships through grants to public or other nonprofit institutions."

Justification

National Institute of Child Health and Human Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 478 | $4,071,000 | 573 | $4,940,000 | +95 | +869,000 |
| Other expenses | ... | 63,964,000 | ... | 70,454,000 | ... | +6,490,000 |
| Total | 478 | 68,035,000 | 573 | 75,394,000 | +95 | +7,359,000 |

General Statement

The National Institute of Child Health and Human Development, unlike those Institutes which are primarily concerned with one category of diseases or part of the body, seeks to acquire new knowledge and deeper insight into the array of health problems and requirements of mothers and children, and into the nature of the developmental processes of all individuals throughout the life span. The over-all, long-range objective of the Institute is improvement in the quality of human existence through greater scientific understanding of the developmental processes.

The Institute is requesting $75,394,000 for 1969, an increase of $7,359,000 over 1968. This increase will be used primarily for three purposes: (1) $2,000,000 for the support of research to be conducted in the newly constructed Mental Retardation Research Centers; (2) $1,595,000 for intramural research, particularly to staff and equip the new Gerontology Research Center in Baltimore; and, (3) $3,500,000 for expansion of the contract program in reproduction and population research and fertility control

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Regular projects..... | $37,583,000 | $37,583,000 | ... |
| Special program..... | 4,864,000 | 6,682,000 | +1,818,000 |
| Total, research grants | 42,447,000 | 44,265,000 | +1,818,000 |

Introduction:

This activity supports regular research grant projects in reproduction and population, perinatal biology and infant mortality, growth and development, adult development and aging, and mental retardation. In addition, funds are provided for general research support grants, scientific evaluation grants, categorical clinical research center grants, and mental retardation research center grants.

In 1968, the Institute plans to support approximately 1,122 regular research projects in the amount of $37,583,000. Most of these projects are ongoing noncompeting continuation grants which were approved for payment by advisory groups in 1967 and prior years. The noncompeting continuation grants represent approximately 70% of the total regular research programs.

In 1969, The Institute plans to support 39 more competing awards than are to be funded in 1968. By the end of 1969, eight Mental Retardation Research Centers will be in operation. $2,000,000 is requested in 1969 to support research in these new centers.

Program Plans for 1968 and 1969:

Reproduction and Population Research:

The Institute's overall program in reproduction and population research is broadly based and includes the research areas of reproductive biology, development of contraceptives, the psychological and social aspects of reproduction and fertility regulation, and the application of epidemiology to family planning programs. Most of the grants held by NICHD in these fields support projects in reproductive biology, and contracts are used to support projects in the other areas. This arrangement has occurred because fundamental research in reproductive biology is a well established scientific field with a number of qualified investigators, whereas the scientific importance of the other fields has been recognized only recently. These other fields warrant, therefore, the special attention available to them through collaborative programs.

The grant program in reproduction and population research is devoted primarily to studies which will add to fundamental information on the biological and behavioral processes of reproduction in humans and experi-

mental animals. Many of these studies are part of the Institute's programs in population research because it is clear that meaningful advances in population research are dependent upon the continued acquisition of information concerning the reproductive process.

Reproductive biology includes investigation of the development of germ cells in the male and female, ovulation, the processes of fertilization, oviduct transport, implantation in the uterus, and studies of the physiological, endocrine and neuroendocrine factors influencing these processes. Studies of ovulation include projects on the maturation of ovarian follicles, and the biochemical and biophysical factors involved in ovum release, as well as attempts to improve the detection of ovulation by such methods as luteinizing hormone or temperature measurement. Research on male germ cells includes work on spermatogenesis, sperm metabolism, and sperm antigens in relation to male infertility or as a potential method of fertility control. There are a number of projects on factors involved in sperm transport and sperm capacitation in the female reproductive tract and on the effects of oviductal and uterine secretions.

Reproductive endocrinology includes studies of hypothalamic releasing factors, gonadotrophic hormones and sex hormones, and involves work on isolation and structure, biosynthesis, and mechanisms of action in target tissues. A number of investigators are concerned with factors involved in the maintenance or lysis of the corpus luteum. Embryological studies deal with differentiation, embryonic induction mechanisms, and biochemical differentiation. There are a number of studies of cell structure, cell division, and cell differentiation. The reproductive biology program also includes a number of studies in genetics, some of which are clinical investigations in biochemical or cytogenetics, while others are more basic and deal with chromosome structure and function in lower forms. Finally, there is also some behavioral and social science research in the reproduction program, including studies of sex behavior and of factors controlling animal population density, as well as demographic studies of human fertility.

Perinatal Biology and Infant Mortality:

A major concern of this Institute is the stimulation and support of fundamental research which relates to various aspects of maternal and infant health. New knowledge must be achieved which will make possible the realization of maximum health and well being for every pregnant women and her progeny. In order to achieve this goal, the Institute has developed a research program evolving around the broad areas of pregnancy maintenance, management, and termination; intrauterine fetal survival and well being; extrauterine adaption; and disorders of infancy. Since the two major causes of infant mortality are neonatal respiratory distress syndrome and prematurity, the Perinatal Biology and Infant Mortality Program will emphasize a multifaceted attack upon the specific problems involved in each of these two areas.

Each year in this country, some 300,000 infants are born weighing 5 1/2 pounds or less, and must wage an uphill struggle for survival and normal health.

For more than 42,000 of these infants each year the battle is a losing one, and they die during the neonatal period. Should the infant survive these first difficulties and others related to intrauterine life and the process of birth, long periods of expensive hospitalization and nursing care are frequently required before the infant can be cared for at home. Each year, Americans spend an estimated $500,000,000 for such hospital care services, not including continued constant care which is often necessary for infants severely brain damaged or crippled at birth.

To prevent this tremendous waste in human life and the expenditure of millions of dollars yearly, there is a pressing need for research into the nature, causes, and sequelae of prematurity and intrauterine growth retardation. These are, for the most part, still obscure.

Until we can fill these gaps, low birth weight will remain an outstanding child health problem. The National Institute of Child Health and Human Development Perinatal Biology and Infant Mortality Program, through development of an integrated program of research and training, is seeking to accomplish four major objectives, as part of its efforts to gain new knowledge of, and solutions to, problems associated with low birth weight. These are: 1) a means of prolonging gestation to term with optimal prenatal development of the fetus before birth; 2) because prolongation is not always feasible an understanding of the immature systems and adaption processes of premature babies so they will receive the best possible care; 3) identification of reliable indices of fetal and neonatal maturation; and 4) prevention and/or correction of intrauterine growth retardation.

Studies of extrauterine adaptation will be devoted to research concerning the respiratory distress syndromes, including hyaline membrane disease. This is a common cause of death among the newborn, especially premature infants, and yet its pathogenesis remains a mystery and its treatment empirical and frequently unsatisfactory.

If greater understanding of the problems of respiratory distress in the newborn is to be achieved, much greater emphasis must be placed on scientific study that will contribute new knowledge about embryology, anatomy, and physiology of the normal developing lung and will also identify those factors that may be controlled to prevent the development of this syndrome. We need also to find methods by which to improve pulmonary vascular function in infants with respiratory distress syndrome.

Thus, future program plans will emphasize activities directed toward the identification of the cause, treatment, and prevention of this syndrome. If it were possible to prevent or to treat adequately this syndrome, a significant inroad into our present infant mortality problem would be accomplished.

Growth and Development:

The Institute-supported research in growth and development is concerned with the period of development extending from birth to adulthood. The ultimate goal is the enhancement of individual capabilities through an understanding of the factors, both biological and behavioral, contributing to human variability and optimal development. The biological aspects of human development which will receive special emphasis in 1968 and 1969 include studies related to the malnourished child and to the process of biological maturation.

Current data suggest that children are maturing at an earlier age. Not only is this of considerable interest insofar as physical size and sexual maturation are concerned, but it may be importantly related to questions of physical fitness and preparation for adult life. Laboratory, clinical and field studies will be conducted to define more precisely the relationships between chronologic age and indicators of biologic age such as bone formation and secondary sexual characteristics. Special emphasis will be given to developing specific growth standards for all segments of the population and to devising accurate methods for predicting ultimate stature on the basis of measurements made at an early age. Investigations of essential factors in maintaining optimal performance in daily life will be undertaken. These will include studies of the development of resistance to disease, the need for balanced schedules of rest and exercise, and the capacity of various organ systems to cope with normal and adverse conditions.

Further definitions of normal hormone production and action as they relate to biological growth and development will be sought. Of particular importance will be investigations of the endocrine glands, and their interaction with neural and environmental stimuli.

The problem of malnutrition will also receive special emphasis in 1969. A series of interrelated studies will be undertaken with undernourished and disadvantaged children to define the association between nutritional status and intellectual development. In addition, studies will be initiated to evaluate nutritional intervention programs applicable to this problem. Attention will also be given to nutritional factors in brain and nervous system development, as well as to those critical periods when improper nutrition may inflict the greatest damage.

In approaching the complexity of human development from the behavioral standpoint, research on maximizing the capacity of the individual to learn will receive primary emphasis. The success of our society now rests and will continue to rest on the degree to which individuals can learn new skills and adapt to new challenges. This will require expansion of our knowledge concerning how man learns and how the learning process can provide maximal fulfillment for each child. To the extent that functional illiteracy and impaired learning potential prevail, and to the degree to which the gifted persons are not given special opportunities to realize their full potential, our culture will fail to make maximal progress.

It is apparent that impoverished environments inhibit the development of learning and adaptive processes. The mechanisms for these effects are not known. A broader base of fundamental knowledge concerning psychological development and learning is needed. A greater understanding of the role of early stimulation and deprivation on cognitive development will be sought, as will the consequences of social deprivation on brain structure and function.

Special emphasis will be given to determining at what age inadequate intellectual development becomes permanent and irreversible. Attention will be given to the development of measures for evaluating present and future improvement on learning ability as new discoveries and techniques improve learning capacities.

Biological and behavioral research will be directed towards a better understanding of the factors contributing to normal development of speech and language functions and the role these skills play in the development of individuals as members of society. With this knowledge, reading and speaking disorders may be prevented or ameliorated and children will be able to acquire greater speech, language, and reading facility than at present.

A second area of concentration in behavioral studies is the problem of youth in a mass society. As the American society becomes more complex, as our cities become more crowded, as schools attempt to face problems of increasingly complex technical education and of heterogeneous student bodies, our understanding of how children and youth develop into contributing members of society must increase. For example, a better understanding is needed of how children respond to diverse and sometimes conflicting social influences arising from parents, peer groups, mass media, schools and other socializing forces. Particular attention will be given to examining ways in which various social institutions combine to influence the development of skills and values needed to meet, constructively, adult responsibilities. A better understanding will be sought of the factors leading to social and emotional problems among adolescents, particularly as expressed through aggressiveness, irresponsibility, and impaired character development.

Adult Development and Aging:

Biomedical aging is a subtle process operating from early life and acting as a major determinant of human health. The mechanisms of biomedical aging are only beginning to be understood, but its consequence has long been known. That consequence is increased valnerability to disease. That vulnerability as judged by the mortality rate, reaches a low point at 10 year of age and thereafter doubles every 8.7 years.

The result of biomedical aging are most distressing in persons over 65. There are 19 million of these persons in our country today making up almost 10 percent of the population. Although the results of biomedical aging are most distressing in persons over 65, aging

itself begins with the attainment of maturity if not earlier. If man is to understand the processes involved, he must study them across most of the lifespan. As the major diseases are coming to be understood, ignorance of aging processes stands out in bold contrast. Comprehension of th se processes will greatly deepen our understanding of the diseases that occur in man as he ages. Biomedical science will be incomplete until the biological aspects of aging are understood.

Research grants in 1969 will support work on biomedical research at the level of the entire organism and at the cellular level. Changes with age in the coordinated function of the individual and in the function of the various organ systems - - cardiovascular, pulmonary, renal, etc.,-- will be investigated. Cross-sectional and longitudinal research, in which humans are intensively studied over a period of years, provides the ideal approach to such changes. It is important to realize that the alterations that occur in function across the years may not be immutable and independent of lifestyle and environment. Much needs to be done to distinguish the contributions of various factors to changes in function. It is known, for example, that half the people over 50 years of age have diabetic glucose tolerance curves by the commonly accepted standards. It is not known whether this is due to an immutable aging or other process. Culturally determined muscular inactivity and dietary practice may contribute much to the observed intolerance of older persons to carbohydrates.

Alterations with age in function at cellular and molecular levels will be studied. Some studies of cell function can be made in the intact organism, but incisive experimental analysis is difficult in whole organisms. The discovery that normal human cells are not immortal in tissue culture provides an analytic approach to cellular senescence that will be pursued.

Psychosocial research on aging is of major importance to the healthy function of the individual and of society. The situation here is more complex than in biomedical research. After the attainment of maturity the effectiveness of certain psychological functions diminishes with age. However, the accumulation of experience leads to continued improvement of some complex functions until relatively late in the lifespan. Research grants will support studies of age changes in intellectual performance and personality, and the factors that affect them favorably and unfavorably. Attention will be given to the psychological needs of the latter year of life and to the effect of the environment upon the life of the elderly. The problems of retirement and of housing are important in this connection. The psychological environment of man changes as he ages in ways that are not always favorable to continued psychological growth. The intellectual challenge of the school years may be replaced by work situations that provide no stimulation to further mental growth. Early, obligatory retirement may further impair the psychological environment.

The age structure of a society is one of the major determinants of how that society functions. Little research on the implications of that structure for the medical, social, and economic activites of the nation has been carried out. Research in this area will be encouraged.

Mental Retardation:

Mental Retardation is unique because the biological, behavioral and social component of mental retardation are so closely interrelated. In recognition of this the Institute has helped develop a Mental Retardation Research Centers program whose primary objective is to provide qualified institutions with a facility and an environment in which a cohesive program of research and research training in mental retardation and related aspects of human development can be accomplished. As of June 30, 1967 the center construction grant program was virtually complete with construction grant awards for centers having been made to the following twelve institutions: Albert Einstein College of Medicine; University of Washington; Children's Hospital, Cincinnati, Ohio; Walter E. Fernald State School, Waltham, Mass.; Geroge Peabody College for Teachers, Nashville, Tennessee; University of California at Los Angeles; Children's Hospital Medical Center, Boston, Massachusetts; University of Kansas; University of North Carolina; University of Chicago; University of Colorado Medical Center, Denver, Colorado; and the University of Wisconsin.

When operational, the Mental Retardation Research Centers will carry the main thrust of the Institute's efforts to solve the problem of mental retardation, through developing a better understanding of the causes, prevention, decection, diagnosis and treatment of mental retardation.

The Institute is concentrating its research efforts on identifying the social and cultural factors underlving the causes of Mental Retardation. An overwhelming majority of the retarded (approximately five million children and adults) are concentrated in the lowest socioeconomic segments of society. Despite the fact that a significant proportion of this group has no discernable central nervous system abnormality, comparatively little formal study has been undertaken to differentiate from among the multiple variables those which have etiological significance. Current efforts to promote the intellectual growth of disadvantaged children have been focused largely on preschool enrichment approaches, early academic training and motivational techniques. The limited success attained thus far by these techniques encourages further study.

Research efforts will be directed toward the discovery of patterns, language development and communication styles, nutritional deficiences, genetics, learning processes and other elements which may be essential to effective intervention programs. Examples of specific research in this area include: the modification of child rearing practices, parental attitudes and interpersonal behaviors within the family; the effect of positive reinforcement and incentive systems on learning and adaptive behavior; the development of methods and procedures to improve functions involving the integration of sensory imput, attending behaviors, perception, motivation, symbolic and linguistic mediation; the role of intelligence in the process of socialization; innovation in methods and content of instruction in early childhood; a

study of cognitive and learning processes, including the biochemical correlates of learning and memory and the search for psychopharmacological agents which may improve learning ability; genetic determinants of intellectual ability; a determination of the relationship of values, technology and social organization to patterns of care, training and rehabilitation for culturally disadvantaged children.

The Institute's second approach to attacking the problem of mental retardation, i.e. research aimed at early detection and diagnosis of the problem, will center around the epidemiology and identification of mental retardation. The earliest possible identification of children who are or who may become retarded is critical to preventive and ameliorative efforts. The development of new diagnostic procedures and the refinement of established procedures can assist in this objective. Adequate data do not exist on the incidence or prevalence of mental retardation in general or with respect to specific diagnostic classifications. Surveys are hampered by problems of definition and data collection activities have been directed toward specific subgroups rather than representative samples of the population. Clinical research to improve better understanding of the patterning and interaction of related variables is needed. Examples of specific research which the Institute plans to support in this area include: studies of birth cohorts, special population groups, and case materials, retrospective and prospective, with respect to seasonal factors, genetic conditions, epidemics, etc.; the development and analysis of extensive profiles on institutional populations as a basis for follow-up investigations on causal factors; and establishment of diagnostic procedures to identify early signs of central nervous system damage.

Research aimed at treatment and amelioration of mental retardation consitutes the Institute's third approach to the problem. Much evidence exists today that intelligence and adaptive behavior--the two dimensions by which mental retardation is defined--result from the subtle interaction of biological and social environmental factors. Both traits are alterable characteristics, subject to change through a variety of psychoeducational, therapeutic and social intervetion procedures. The nature of these precedures, however, and the principles and mechanisms which underlie them, are as yet incompletely understood. The research program will attempt to specify more precisely the treatment and intervention techniques that will maximize the retarded person's level of functioning and m o d i f y his impact on the family and community. Such studies must include the following; preschool enrichment; basic learning processes and methods of instruction; cognition and perception; sensory-motor integration; family behavior modification; social organizations, institutions and structures; and public, professional and parental attitudes.

## Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting projects | 870 | $26,225,000 | 831 | $24,191,000 | -39 | $-2,034,000 |
| 2. Competing projects | 252 | 11,358,000 | 291 | 13,392,000 | +39 | +2,034,000 |
| 3. Subtotal regular program | 1,122 | 37,583,000 | 1,122 | 37,583,000 | ... | ... |
| 4. General research support | | 4,264,000 | | 4,082,000 | | -182,000 |
| 5. Scientific evaluation | ... | 100,000 | ... | 100,000 | ... | ... |
| 6. Categorical clinical research centers | ... | 500,000 | ... | 500,000 | ... | 500,000 |
| 7. Mental retardation centers | ... | ... | ... | 2,000,000 | ... | +2,000,000 |
| 8. Total research grants | 1,122 | 42,447,000 | 1,122 | 44,265,000 | ... | +1,818,000 |

## Research Grants Program Analysis

| | | | |
|---|---|---|---|
| 1. Reproduction & Population Research | $8,084,000 | $8,084,000 | ... |
| 2. Perinatal Biology & Infant Mortality | 9,268,000 | 9,268,000 | ... |
| 3. Growth and Development | 12,523,000 | 12,523,000 | ... |
| 4. Aging | 3,303,000 | 3,303,000 | ... |
| 5. Mental Retardation | 4,405,000 | 4,405,000 | ... |
| 6. Subtotal regular program | 37,583,000 | 37,583,000 | ... |
| 7. General research support | 4,264,000 | 4,082,000 | -$182,000 |
| 8. Scientific evaluation | 100,000 | 100,000 | ... |
| 9. Categorical clinical research centers | 500,000 | 500,000 | ... |
| 10. Mental retardation research centers | ... | 2,000,000 | +2,000,000 |
| 11. Total research grants | 42,447,000 | 44,265,000 | +1,818,000 |

Fellowships

| | 1968 Estimates | 1969 Estimates | Increase or Decrease |
|---|---|---|---|
| Total Fellowships ..... | $4,102,000 | $4,193,000 | +$91,000 |

Introduction:

The fellowships program for the National Institute of Child Health and Human Development reflects a net increase of $91,000 in 1969 over 1968, including an increase of $223,000 to support an additional 12 non-competing continuations and $69,000 for an additional 7 competing continuations. This is offset by a decrease of $201,000 from the 1968 level of new fellowship awards.

The net increase of $91,000 will be used for an additional 6 special fellowship awards;, postdoctoral, research career and research career development awards will remain at the same level in 1969.

Program Plans for 1968 and 1969:

The National Institute of Child Health and Human Development training committees recognize the fellowship program as a unique opportunity for the development of personnel for careers and research investigators. It is a highly flexible program providing individuals at different stages of development with support for research training in selected areas. As a mechanism it is well suited to support more senior individuals and is most effective in directing and developing scientists in the terminal phase of their training. This program is of considerable significance to the Institute as a means of encouraging individuals to develop a cross-disciplinary approach. Such an approach is most desirable for an Institute which is dedicated to the study of the organism through certain phases of its development, rather than the study of categorical diseases areas.

The type of fellowships awards funded by the National Institute of Child Health and Human Development in the past will again be given strong priority in 1968 and 1969 because of the ever-increasing demands of research in these fields. Of prime importance is the training of obstetricians, gynecologists, and pediatricians. One of the National Institute of Child Health and Human Development's special research problems is a lack of trained clinicians--scientists who approach the investigation of health problems from the standpoint of human observation rather than controlled experiments. Gynecology, obstetrics and pediatrics are the clinical specialities which relate most frequently to the National Institute of Child Health and Human Development's particular interest in the health problems of mothers and children. There are too few pediatricians and obstetricians now, even to supply the nation's medical care needs. It is therefore essential that the total number be increased rather than any be diverted from clinical care to research.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | NNo. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting | 131 | $2,515,000 | 143 | $2,738,000 | +12 | $+223,000 |
| b. Competing | 17 | 244,000 | 24 | 313,000 | +7 | +69,000 |
| 2. Supplementals | (6) | 5,000 | (6) | 5,000 | ... | ... |
| 3. New | 121 | 1,338,000 | 108 | 1,137,000 | -13 | -201,000 |
| 4. Total fellowships | 269 | 4,102,000 | 275 | 4,193,000 | +6 | +91,000 |

Fellowships by type of program

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Postdoctoral | 109 | $946,000 | 109 | $946,000 | ... | ... |
| 2. Special | 57 | 779,000 | 63 | 870,000 | +6 | $+91,000 |
| 3. Research Career: | | | | | | |
| a. Career | 8 | 240,000 | 8 | 240,000 | ... | ... |
| b. Development awards. | 95 | 2,137,000 | 95 | 2,137,000 | ... | ... |
| 4. Total fellowships | 269 | 4,102,000 | 275 | 4,193,000 | +6 | +91,000 |

Fellowship Program Analysis

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| 1.Reproduction & population research | $1.157,000 | $1,234,000 | $+77,000 |
| 2.Perinatal biology & infant mortality | 886,000 | 886,000 | ... |
| 3.Growth and development | 1,404,000 | 1,404,000 | ... |
| 4.Aging | 336,000 | 343,000 | +7,000 |
| 5.Mental retardation | 319,000 | 326,000 | +7,000 |
| 6. Total fellowships | 4,102,000 | 4,193,000 | +91,000 |

## Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total Training Grants ..... | $9,762,000 | $10,012,000 | +$250,000 |

Introduction:

This activity provides for grants to institutions for support of graduate students in the fields of reproduction and population research, perinatal biology and infant mortality, growth and development, aging, and mental retardation.

The increase of $250,000 in 1969 over the 1968 level includes $102,000 to support one additional noncompeting continuation, $36,000 to support one additional competing continuation, and $112,000 to fund two additional new training awards.

Program Plans for 1968 and 1969:

NICHD research training programs seek to produce researchers who will have the skills and the interest to expand our present inadequate understanding of the complex phenomena which characterize development of the human organism, not only in terms of his physical form and function, but also in terms of his mental, emotional, perceptual, intellectual, and social development. This knowledge is essential for rational solutions to the human problems which confront the NICHD, and for efficient and systematic approaches to such solutions. The mixture of basic, clinical and applied research requires highly trained scientists in both clinical and non-clinical disciplines. There is an acute shortage of highly trained professionals in each of the Institute's five major program areas.

Reproduction and Population Research:

The field of reproduction research requires researchers trained in a wide range of disciplines. One of the most urgent needs is for scientists trained in reproductive biology--an area which encompasses endocrinology, biology, physiology, gynecology, and other disciplines. There is also a great need for behavioral scientists in the field, to determine those factors which influence such important decisions as the type of contraceptive method used, if any; the size of the family; and the effects of careful spacing of children.

In its approach to the population growth problem, the Institute is also supporting training in a broad spectrum of scientific research fields ranging from cell biology to demography.

Perinatal Biology and Infant Mortality:

The Institute serves as a focal point for the coordination, stimulation, and support of a broad program of research which will encompass all aspects of normal and abnormal reproduction, pregnancy and infant survival and well being. This research program necessitates trained scientists in such fields as immunology, since infectious disease is an important underlying condition of death in the neonatal period; genetics, since congenital malformations, defects and death in the fetus and newborn often stem from hereditary causes; and behavioral sciences, since such factors as maternal education and attitudes, urban-rural status, social status, family income, sanitation and housing have a high influence on infant death. Epidemiologic training is also needed to develop studies of sudden unexplained infant death, and to survey those segments of the population whose rate of infant death is greatest.

Growth and Development:

Since this research program is concerned with the period from birth to adulthood, the training needs must necessarily be expansive. Many biological and behavioral areas are called into play including biochemistry, anatomy, physiology, nutrition, sociology, psychology and neurology. Since childhood, perhaps more than any other period, involves an interaction of many factors, the researchers must possess broad training in several disciplines. There is a great need for researchers who are competent to evaluate congitive and perceptual development and personality functions as they relate to biological growth and optimal human development.

Adult Development and Aging:

The most significant factor in the present lack of trained professionals engaged in aging research is the comparatively recent emergence of gerontology as a scientific discipline. The U.S. Public Health Service established a unit on gerontology only shortly before World War II, and gerontologists formed their own society barely twenty years ago.

No medical school has a department of gerontology, and the scientist interested in studying aging must look to the established disciplines including biochemistry, psychiatry, pathology, physiology, and molecular biology for career advancement.

The Institute has in the past two years contracted with a major gerontological organization to investigate means of encouraging young scientists to seek additional training in gerontological fields and to promote better curricula for this type of training. A start has been made, but the training base is so small compared with the research needs that the problems confronting this field can be met only with major emphasis on gerontological training.

Mental Retardation:

The construction of the new Mental Retardation Research Centers is greatly increasing the demands for skilled professional personnel. The dearth of trained manpower represents the most important signle obstacle to the establishment and expansion of urgently needed facilities and for the implementation of research activities within them. This shortage extends to all disciplines and all kinds of research service and training activities. The NICHD, by its very nature, is concerned with many scientific disciplines, thereby necessitating the most comprehensive training base possible. This need for comprehensive training can be seen in the broad spectrum of scientific disciplines involved in the study of Mental Retardation which includes virtually every biomedical and behavioral discipline.

## Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Decrease or Increase | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting | 119 | 8,699,000 | 120 | 8,801,000 | +1 | +102,000 |
| b. Competing | 8 | 471,000 | 9 | 507,000 | +1 | +36,000 |
| 2. Supplementals | (1) | 55,000 | (1) | 55,000 | (...) | ... |
| 3. New | 7 | 437,000 | 9 | 549,000 | +2 | +112,000 |
| 4. Scientific evaluation | (3) | 100,000 | (3) | 100,000 | (...) | ... |
| 5. Total training grants | 134 | 9,762,000 | 138 | 10,012,000 | +4 | +250,000 |

## Training Grants (By type of program)

| | 1968 Estimate | | 1969 Estimate | | Decrease or Increase | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate | 134 | $9,662,000 | 138 | $9,912,000 | +4 | $+250,000 |
| 2. Scientific evaluation. | (3) | 100,000 | (3) | 100,000 | ... | ... |
| 3. Total training grants. | 134 | 9,762,000 | 138 | 10,012,000 | +4 | +250,000 |

## Training Grant Program Analysis

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| 1. Reproduction & population research. | $3,094,000 | $3,173,000 | $+79,000 |
| 2. Perinatal biology & infant mortality | 925,000 | 925,000 | ... |
| 3. Growth and development | 2,800,000 | 2,800,000 | ... |
| 4. Aging | 1,874,000 | 1,922,000 | +48,000 |
| 5. Mental retardation | 969,000 | 1,092,000 | +123,000 |
| 6. Subtotal, regular program | 9,662,000 | 9,912,000 | +250,000 |
| 7. Scientific evaluation | 100,000 | 100,000 | ... |
| 8. Total training grants | 9,762,000 | 10,012,000 | +250,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 271 | $2,184,000 | 354 | $2,956,000 | +83 | +$772,000 |
| Other expenses | | 2,914,000 | | 3,737,000 | | + 823,000 |
| Total | 271 | $5,098,000 | 354 | $6,693,000 | +83 | +$1,595,000 |

Introduction:

Seven laboratories and branches--Reproduction Research Branch, Developmental Biology Branch, Laboratory of Biomedical Sciences, Children's Diagnostic and Study Branch, Behavioral Biology Branch, Social and Behavioral Sciences Branch, and Gerontology Research Center--conduct the Intramural Research operations in the program areas listed below. The funds requested for laboratory and clinical research by these units represents a program increase of $550,000 in 1969 over 1968. Other increases include $383,000 for 1969 annualization of positions new in the 1968 President's Budget, $25,000 for 1969 annualization of the 1968 pay raise costs and $14,000 for one additional day of pay in 1969. Also included is an increase of $623,000 for centrally furnished services from the National Institutes of Health Management Fund."

Program Plans for 1968 and 1969:

The office of the Associate Director for Intramural Research will staff a clinical facility which will become available to the Institute during 1969. These clinical resources will have input from four of the five Institute program areas: Reproduction and Population, Perinatal Biology and Infant Mortality, Growth and Development, and Mental Retardation. However, the limitations of resources will make it necessary to place emphasis on only one of these program areas at one time. The remaining program area, Adult Development and Aging, has independent clinical resources.

Reproduction and Population:

Support will continue at the same level for studies on human menstruation and pregnancy, analyses of hormonal mechanisms affecting sperm and egg production, fertility and reproduction, production and metabolism of placental hormones, and related studies. Establishment of an obstetrical unit in a teaching hospital will move us a step closer to a comprehensive program of coordinated clinical, laboratory and epidemiological studies of reproductive phenomena in man. Emphasis is being given to fertility control, sterility, gonadal development and pubescence, menopausal and post-menopausal phenomena, disorders of menstrual function and normal and abnormal pregnancies.

Perinatal Biology and Infant Mortality:

The current lines of attack deal with: implantation (ectopic pregnancy); abnormalities related to the pregnancy period including placenta praevia, abruptio placenta, hydatidiform mole and choriocarcinoma; the consequences of infectious episodes at different stages of embryonic and fetal life (including studies of the effect of virus infections, and studies of the development of the immune system); developmental pharmacological studies (development of liver systems for detoxifying drugs, short and long term effects of drugs on embryos and fetuses); and experimental evaluation of the contribution of the egg age to the hazards associated with increasing maternal age.

The Intramural Research Program will investigate possible permanent behavioral modifications produced by the administration of drugs and medicinals during embryonic and fetal development and analyze genetic and biochemical defects, many of which first come to light at birth.

Growth and Development:

Studies in this area range from the biochemical level of organization to the behavioral level. Current studies include fundamental investigations of mechanisms regulating carbohydrate metabolism (insulin, glucagon) the normal and modified development of behavior in embryos, the development of prenatal electrical activity in the brain, the development of verbal behavior in preschool children, the relationship between environmental deprivation and intellectual and personality development, and the interrelationships between cognitive and personality functions in preschool children. Some of the latter studies are being conducted in the context of the Headstart program. During 1969 support for Growth and Development programs will remain at the 1968 level. This is the result of deliberate programming which makes provision for a period of consolidation, and for urgently needed growth in other areas of the Intramural Research Programs.

Adult Development and Aging:

The new Gerontology Research Center will be occupied by existing programs during February and March 1968. By the beginning of FY 1969, the intramural research space in this building and the programs projected for this space should be approximately half staffed. Staffing of the programs and facilities of the Gerontology Research Center take high priority in the Intramural Programs of the Institute. The increase of 40 positions will permit interior expansion of: the longitudinal program (in depth studies of over 500 aging human males); studies in molecular biology which seek the basic mechanisms underlying the aging process; studies in cellular and comparative physiology which seek to define the biochemical concomitants of aging; and a range of basic investigations in animals which allow greater latitude in experimental design.

Mental Retardation:

The activities of the Intramural Research Program in the area of mental retardation are principally represented by the Children's Diagnostic and Study Branch. This clinically oriented unit is bringing to bear a battery of clinical specialties on a population of mentally retarded children in a three-step program which seeks to improve diagnoses, identify precipitating factors and, ultimately, to develop preventive and restorative procedures. During 1969, the resources of the unit and of this program area will be approximately the same as they were in 1968, and will permit the Intramural Research Programs to develop other areas .

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 34 | $333,000 | 39 | $381,000 | +5 | +$48,000 |
| Other expenses | | 1,197,000 | | 4,651,000 | | +3,454,000 |
| Total | 34 | 1,530,000 | 39 | 5,032,000 | +5 | +3,502,000 |

Introduction:

This activity serves the important purpose of supplementing and complementing the Institute's research programs. It is one of the most effective ways for coordinating program development in the major areas of interest--reproduction and family planning, perinatal biology and infant mortality, growth and development, aging, and mental retardation.

Program liaison is maintained and furthered through support of interdisciplinary research conferences and symposia and through Scientific Information Centers which are being established. In addition, public information activities insure that the Institute's programs and goals are appropriately reflected to interested segments of the public.

Program Plans for 1968 and 1969:

The net increase of $3,502,000 will be used to expand the contract program in reproduction and population research and fertility control and to provide five positions for scientific staff to direct these programs. Maximum emphasis of the contract program will be concentrated in the following three research areas: 1. The medical effects of contraceptives, 2. the development of new contraceptives, and 3. the psycho-social aspects of family planning.

Current studies on the mechanism of action and medical effects of contraceptives and on the methodology needed for surveillance studies will be continued and expanded. Long-term studies are underway on actual and possible effects of oral contraceptives on the development of cervical dysplasia and on carbohydrate and lipid metabolism, and additional proposals are being developed for research on possible carcinogenic and diabetogenic effects as well as for studies of the effects of oral contraceptives on the outcome of subsequent pregnancies.

The funds will also be used to initiate a feasibility study for a coordinated program directed to the development of new contraceptive methods. A number of potentially effective fertility regulation techniques are at a stage where a concentrated research effort may prove especially fruitful and a task force is now engaged in identifying such areas and the research needed to bring them to fruition.

Contract research will be supported in the psychological and social aspects of family planning, including such areas as the social determinants of attitudes toward family size, motivational factors in the acceptability of family planning methods, and the development of methods to measure the magnitude of the problem of unwanted pregnancies.

The net increase of $3,502,000 for Collaborative Research and Development is made up of a program increase of $3,500,000, a built-in increase of $5,000 and a decrease of $3,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Biometry, Epidemiology, and Field Studies

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 23 | $177,000 | 23 | $183,000 | -- | +$6,000 |
| Other expenses | | 1,863,000 | | 1,863,000 | | --- |
| Total | 23 | 2,040,000 | 23 | 2,046,000 | -- | +6,000 |

Introduction:

This activity supports the Institute scientific staff in planning and conducting epidemiologic and biometric investigations and conducts research in epidemiological and biometric theory, techniques and methods. It also collects and analyzes program statistics for various programs and executes statistical studies for use in program planning, development and evaluation.

The net increase of $6,000 includes a $4,000 increase for the annualization of the 1968 pay raise cost, a $1,000 increase for one additional day of pay in 1969, and $1,000 increase for centrally furnished services from the "National Institutes of Health Management Fund."

Program Plans for 1968 and 1969:

The need for sound epidemiologic and biometric studies in the area of reproduction is particularly great. Two epidemiological projects currently being conducted are studies of the characteristics of the human menstrual cycle. In one university, researchers began the menstrual history study in 1934. The study has continued until the present time, accumulating data of over 27,000 person-years of menstrual experience. At present, there are 2,200 women actively collaborating in the study. Data includes information concerning duration of menstruation, and the influences of pregnancies, illness, surgery, drugs, and environment on the menstrual cycle.

The second study involves the menstrual cycles and pregnancies of Eskimo women. It will provide data comparable to the data in the long-range study mentioned above, and will help to assess environmental, cultural, and behavioral influences in the reproductive processes.

Extensive epidemiological studies are also being conducted in the field of Growth and Development. As a result of increasing evidence that severe malnutrition may retard intellectual development, the Institute has

contracted for a field study in Guatemala to investigate the impact of nutrition on intellectual and physiological development. A highly qualified research team has developed new techniques for a multi-disciplinary study assessing physical and intellectual growth in village populations. The use of food supplements has been started within the pilot village. The project is expected to extend over a number of years to permit evaluation of the long-term effects of dietary improvement.

With the exception of a few clinical conditions, relatively little is known today about the frequency and distribution of most forms of mental retardation and the biological and environmental factors with which they are associated. A few of the factors needing epidemiological assessment are: the role of infectious diseases, chromosomal abnormalities, risk factors in pregnancy, and biochemical abnormalities.

A biometric study of great significance is being carried out under a contract with the Western Interstate Commission for Higher Education. Data have been collected on approximately 24,000 residents in 18 institutions for the retarded in the western states. The data gathered comprise the most complete psychosocial profiles on retarded subjects ever collected. The analysis of these data, now underway, will hopefully generate meaningful hypotheses for more intensive study.

Training Activities

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits ..... | 5 | $43,000 | 5 | $43,000 | -- | -- |
| Other expenses ..... | | 46,000 | | 46,000 | | -- |
| Total ..... | 5 | 89,000 | 5 | 89,000 | | -- |

Lack of sufficient numbers of trained scientists has always been a crucial problem. The direct training program is an especially effective means of coping with this problem. The program is geared to the needs of our intramural research operations by providing supplementary or cross-disciplinary training for the Institute's scientific staff members or those who are planning to join the staff.

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 94 | $807,000 | 98 | $822,000 | +4 | +$15,000 |
| Other expenses | | 1,147,000 | | 1,164,000 | | +17,000 |
| Total | 94 | 1,954,000 | 98 | 1,986,000 | +4 | +32,000 |

This activity is composed of professional and supporting personnel who are responsible for the administration of the Institute's several grants activities. This involves planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the problem areas for which this Institute is responsible; the securing of review and evaluation of research and training grant applications for presentation to the National Institute of Child Health and Human Development Advisory Council; required Council staff assistance; liaison with the applicants, grantees, other components of National Institutes of Health, Public Health Service, advisory bodies, and interested organizations; continued surveillance of scientific activities and progress of the research and training grant programs; and recording and reporting of fiscal and scientific information relevant to all grant transactions.

The increase of $32,000 will provide for a program increase of $20,000 to meet increased staff costs due to the added workload in the grant areas, $6,000 for the annualization of positions new in 1968, $10,000 for the 1969 annualization of the 1968 pay raise costs, $3,000 for one additional day of pay in 1969, and offset by a decrease of $7,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 51 | $527,000 | 54 | $555,000 | +3 | +$28,000 |
| Other expenses | | 486,000 | | 523,000 | | +37,000 |
| Total | 51 | 1,013,000 | 54 | 1,078,000 | +3 | +65,000 |

This activity includes the Offices of the Director, Assistant to the Director for Population Research, Associate Director for Planning and Evaluation, Executive Office, Administrative Office and the Budget Office. These offices are responsible for the general administration, direction and coordination of the Institute programs as well as the review of current and proposed operations.

The increase of $65,000 will provide for a program increase of $20,000 to continue effective management of a growing organization, $6,000 for the annualization of positions new in 1968, $6,000 for the 1969 annualization of the 1968 pay raise costs, $2,000 for one additional day of pay in 1969, and $31,000 for centrally furnished services from the "National Institutes of Health Management Fund"

THURSDAY, MARCH 21, 1968.

# ENVIRONMENTAL HEALTH SCIENCES

## WITNESSES

DR. PAUL KOTIN, DIRECTOR
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
GEORGE M. KINGMAN, EXECUTIVE OFFICER, ENVIRONMENTAL HEALTH SCIENCES
ROBERT H. BRAMLET, BUDGET OFFICER, ENVIRONMENTAL HEALTH SCIENCES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 316 | 1,111 | 1,992 |
| Positions other than permanent | 17 | 33 | 22 |
| Other personnel compensation | 1 | 7 | 6 |
| Total personnel compensation | 334 | 1,151 | 2,020 |
| Personnel benefits | 33 | 116 | 208 |
| Travel and transportation of persons | 52 | 116 | 160 |
| Transportation of things | 15 | 51 | 75 |
| Rent, communications, and utilities | 115 | 277 | 350 |
| Printing and reproduction | 2 | 13 | 20 |
| Other services | 173 | 462 | 173 |
| Project contracts | | 700 | 400 |
| Services of other agencies | 100 | | |
| Payments to "National Institutes of Health management fund" | 434 | 1,057 | 1,351 |
| Supplies and materials | 101 | 330 | 328 |
| Equipment | 603 | 245 | 300 |
| Grants, subsidies, and contributions | 10,389 | 12,506 | 12,714 |
| Total obligations | 12,351 | 17,024 | 18,099 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanedt positions | 66 | 171 | 232 |
| Full-time equivalent of other positions | 2 | 3 | 3 |
| Average number of all employees | 38 | 135 | 205 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING

(In thousands of dollars)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| 1. Grants: | | | |
| (a) Research | 6,597 | 8,611 | 8,622 |
| (b) Fellowships | 99 | 100 | 200 |
| (c) Training | 3,693 | 3,795 | 3,892 |
| Total grants | 10,389 | 12,506 | 12,714 |
| 2. Direct operations: | | | |
| (a) Laboratory and clinical research | 620 | 3,749 | 4,538 |
| (b) Review and approval of grants | 270 | 420 | 449 |
| (c) Program direction | 145 | 349 | 398 |
| Total direct operations | 1,035 | 4,518 | 5,385 |
| 3. Adjustment of prior year costs | −1,621 | | |
| Total program costs, funded [1] | 9,803 | 17,024 | 18,099 |
| Change in selected resources [2] | 2,548 | | |
| Total obligations | 12,351 | 17,024 | 18,099 |
| Financing: | | | |
| Comparative transfers to other accounts | 10,634 | | |
| Unobligated balance lapsing | 1,313 | 265 | |
| New obligational authority (appropriation) | 24,298 | 17,289 | 18,099 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 12,351 | 17,024 | 18,099 |
| Receipts and other offsets (items 11 to 17) | 10,634 | | |
| Obligations affecting expenditures | 22,985 | 17,024 | 18,099 |
| Obligated balance, start of year | 12,392 | 18,278 | 18,279 |
| Obligated balance, end of year | −18,278 | −18,279 | −19,378 |
| Adjustments in expired accounts | −141 | | |
| Expenditures | 16,958 | 17,023 | 17,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 7,269 | 7,297 | 7,000 |
| Out of prior authorizations | 9,689 | 9,726 | 10,000 |

[1] Includes capital outlay as follows: 1967, $603,000; 1968, $245,000; 1969, $300,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $2,423,000 (1966 adjustments $125,000); 1967, $4,731,000; 1968, $4,731,000; 1969, $4,731,000.

Mr. FLOOD. Now we have the environmental health sciences. The presentation will be made by Dr. Paul Kotin, the director.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESSES

We have a biographical sketch of the doctor which will be placed in the record at this point.

(The biographical sketch follows:)

Name: Paul Kotin, M.D.
Position: Director, Division of Environmental Health Sciences.
Birthplace and date: Chicago, Ill., August 13, 1916.
Education: B.S., University of Illinois, 1937; M.D., University of Illinois Medical School, 1940; Diplomate, American Board of Pathology, 1953.

Experience:

November 1966 to present: Director, Division of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.

1964–66: Scientific Director for Etiology, National Cancer Institute, Bethesda, Md.

1963–64: Associate Director for Field Studies, National Cancer Institute, Bethesda, Md.

1962–63: Chief, Carcinogenesis Studies Branch, National Cancer Institute, Bethesda, Md.

1960–62: Paul Peirce Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

1959–60; Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

1955–59: Associate Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

1953–55: Assistant Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

1951–53: Instructor in Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

1951–62: Attending Staff Pathologist, Los Angeles County Hospital, Los Angeles, Calif.

1950–51: Medical Microbiologist, Los Angeles County Hospital, Los Angeles, Calif.

1949–50: Research fellow in pathology, University of Southern California, Los Angeles, Calif.

1946–48: Private practice in pathology and internal medicine, San Luis Obispo, Calif.

*Association memberships*: American Association for the Advancement of Science; American Association for Cancer Research; American Association of Pathologists and Bacteriologists; American Institute of Biological Sciences; American Medical Association; American Public Health Association; American Society for Cell Biology; American Society for Experimental Pathology; International Academy of Pathology; New York Academy of Sciences; Sigma Xi.

*Special awards citations, or publications*: Chairman, Gorden Research Conference of Cancer, 1965; Department of Health, Education, and Welfare, Superior Service Award, 1966; Dr. Kotin has authored and coauthored over 100 published papers relating to experimental carcinogenesis, experimental pathology, air pollution, environmental health, and the role and action of environmental agents in the pathogenesis of disease; he presently serves on the editorial advisory board, A.M.A. Archives of Pathology, and is a member of the board of editors, Environmental Research; Fellow of College of American Pathologists and the New York Academy of Sciences.

## General Statement

Mr. Flood. Doctor, you may proceed.

Dr. Kotin. Mr. Chairman and members of the committee, I am privileged to be here to report on the first year's progress of the Division of Environmental Health Sciences and to discuss with you our plans for the future.

The industrial revolution has modified our environment in many ways and to a fantastic extent. It has opened the door to a universe that no previous civilization has known. Our comforts have multiplied and the gross national product has soared. Man, meanwhile, has been almost unmindful of the damage inflicted by technological advances upon natural resources and human well-being.

Only recently has there been a growing awareness of man's ability to influence the interaction between himself and his environment. There is general recognition that past efforts have been slow in developing, current efforts are inadequate, and further delay will surely mortgage the well-being of future generations. To remain master of the astounding potential of this modern world, man must constantly

concern himself with the possible risks as well as the potential benefits of technological change.

In recognition of the problems of environmental health, the Public Health Service has developed major control and research programs. In the case of control programs, the primary aim is the application of today's knowledge to the solution of today's problems using the most advanced technology. Dr. Prindle and other members of the Bureau of Disease Prevention and Environmental Control have discussed these programs with you previously.

In the case of research programs focused in the Division of Environmental Health Sciences, the primary goal is to advance fundamental knowledge and to develop a scientific base that will serve to provide answers to problems that man's interaction with his environment have created and will inevitably generate in the coming decades. It is these programs that I will discuss today.

In brief, the mission of the Division is to unlock the unknown in environmental hazards to man. The major responsibility for the application of this knowledge is vested in other organizations with whom the Division cooperates closely.

## INTRAMURAL RESEARCH

The National Environmental Health Sciences Center, the intramural research program of the Division, has initiated research that permits the simultaneous applications of diverse scientific disciplines and categorical approaches to meet existing needs that are incapable of being met by traditional methods. This interdigitated approach is also most likely to identify and appraise problems as they develop in the increasing tempo of our technological advances.

The seven classes of environmental agents on which we are now initiating research programs are natural products, metal compounds, hydrocarbon reaction products, tobacco smoke constituents, polymer dusts, pesticides, and pesticide synergists.

Research on these agents and their interaction with man's well-being will be concerned with the chronic, the less obvious, and the unexpected effects, but also with the acute and more obvious. Chronic effects are very difficult to associate with a specific causative agent; they are also readily modified by secondary interactions with other agents. Hopefully, by studying these secondary interactions, we may be able to identify and to capitalize upon potentially beneficial modifications.

Multidisciplinary, functional research is underway in cell biology, analytical and synthetic chemistry, pharmacology and toxicology, and the animal science and technology branches at the National Environmental Health Sciences Center.

In addition to extension of ongoing programs in 1969, we are exploring the feasibility of a broadly based epidemiology program. The identification of the bases for variations in response to environmental insults among individuals must be correlated with experimental laboratory data to provide the important principles and generalizations for the development of guidelines for the use of regulatory agencies.

UNIVERSITY-BASED INSTITUTES

The complexity of environmental health problems requires integration of scientific and technical skills wherever available—intramurally at the Research Triangle Park, within the academic community in university-based institutes, or in research departments. Institutes, serving as centers, incorporate specialized skills, specially tailored facilities, and a functional array of disciplines that can be focused upon a defined segment of the total environmental health problem. Research at each institute complements the programs at the others as well as at the national center at the research triangle. Within the availability of our resources, each is designed to be a part of the whole; moreover, major areas of concern are not being duplicated.

RESEARCH AND TRAINING PROJECTS

In turn, both university-based institutes and the National Environmental Health Sciences Center are dependent upon research projects, supported by the Division, that are conducted in academic research departments and other organizations. Emphasis will be continually applied to the identification of physical, biological, and chemical hazards of the environment with particular relevance to human well-being; the evaluation of the significance of environmental agents to the etiology of disease in man, with special emphasis on low-level, long-term exposure to environmental hazards; and to the development of new or improved methology and instrumentation to characterize the biological effects of known and potentially hazardous environmental agents.

As is true in most of the health fields today, one of the greatest needs in the environmental health field is the preparation and training of adequate numbers of research scientists. Accordingly, the Division supports broad and diverse training efforts that will increase the numbers of researchers trained in the sciences underlying and directly involved in various fields of environmental health research; that will enable training institutions to strengthen and enrich their research training capabilities; and that will expand opportunities for environmental health research training in a greater number of graduate institutions throughout the United States. These efforts are supported by utilizing both the fellowship and training grants mechanisms, which result in a wider selection of training disciplines, faculty sponsors, and geographic locations.

In summary, the Division of Environmental Health Sciences looks outward as much as it looks inward. We are utilizing research resources across the Nation not only through formal links just described, but also by informal bridges to many other organizations and scientists. Also, liaison staff at the National Center maintain intimate contact with program planning and current operations and needs of the regulatory and control programs of the service.

SUMMARY OF BUDGET

To meet the program needs described in this statement, Mr. Chairman, we propose a budget of $18,099,000. The comparable operating level for 1968 is $17,024,500. Increases requested for 1969 include

$11,000 for research grants, $100,000 for fellowships, $97,000 for training grants, and $866,500 for direct operations.

I shall be happy to answer any questions.

Mr. FLOOD. You are asking for a pretty modest increase. You had an appropriation of $17,289,000 for 1968. You want $18,099,000 for 1969. Now believe it or not, as I see this, this request is over $2.5 million less than you requested last year. For me to say this is most unusual is something of an understatement. What is the reason for your loss of ardor? Are you suffering from the aging process our friends from the other institute just talked about?

What is the matter with you?

Dr. KOTIN. The matter with me, I suspect, is the result of a series of circumstances over which we have had very little control.

First, a facility development program and schedule which was evolved many years ago has proven to be obviously quite unrealistic in terms of present constraints.

Mr. FLOOD. How long have you been onboard?

Dr. KOTIN. The Division was activated November 1, 1966, and I am its first Director.

The roots of the Division of Environmental Health Sciences, however, developed over the past decade. When the recommendations and organizational plans were made for its structuring, a much more rapid pace of expansion was realistically then projected; and time, of course, has had its effect.

Mr. FLOOD. Is this an apology?

Dr. KOTIN. Quite to the contrary, it is a complaint.

### LABORATORY AND CLINICAL RESEARCH

Mr. FLOOD. There is barely sufficient increase here in your grant program to cover the increased cost of doing business. But there is the other side of the story. You are asking for a program increase of $489,000 and 54 jobs for laboratory and clinical research. This is for the establishment of an electron microscopy and instrumentation development program. Why do we need to set up this new program?

Dr. KOTIN. The coming year will see the availability of one additional building in the Research Triangle area currently occupied by the National Center for Health Statistics. That organization will be moving to a new site for which ground has been broken. This additional space will permit us to activate the next phase or the next link in the chain of progression.

By contrast with the increase in our extramural programs, it is a large figure. The availability of that additional space will permit the activation of research programs which, for a lack of it, we were forced to defer a year ago.

Staffing of the building will be completed within a relatively short time. Its importance to on-going programs—the resource it represents in the on-going research program—is so crucial that it has one of the highest priorities of all our activities in the National Center.

Mr. FLOOD. What makes you think you can get these 54 people? I thought these highly trained people were hard to get. Where are you going to get 54 people like this?

Dr. KOTIN. They are really not too easy to get. If I may say, the committee expressed much the same concern over recruitment a year ago, as you remember.

Our recruiting, however, within the framework of the high standards of the National Institutes of Health has been successful. Our projections of a year ago have been met, and I have no doubt they will be met this coming year.

Mr. FLOOD. Dr. Shannon, how much piracy do your Institute Directors indulge in behind your back?

Dr. SHANNON. We pirated Dr. Kotin from the Cancer Institute. He, in turn, is going to pirate more people from the Cancer Institute. While we deplore this in on-going programs, we do not deplore taking advantage of the highly specialized skills of people who are available when we start a new activity. We look with favor, particularly if it involves an opportunity to expand the scientific capability of the individual concerned; and this, indeed, will be the case with the people who move from NIH down to the North Carolina Triangle.

I might say that we deplore piracy in the ordinary sense of the word. We do not allow lateral transfers from one Institute to another to be accompanied by a salary increase until the individual has proved out for a year in his new job. If he can do the job, then we will consider a salary increase. We do everything we can to prevent shuttling back and forth simply for purposes of salary improvement.

### UNIVERSITY-BASED ENVIRONMENTAL HEALTH SCIENCE INSTITUTES

Mr. FLOOD. I find this expression: "University-based Environmental Health Science Institutes." What are they? And what is your budget for this year and next year on these impressive-sounding things?

Dr. KOTIN. Happily, their function is as impressive as their name would suggest. What they represent essentially is a coalescence of a series of disciplines and approaches—biological and technical—to problems of environmental health, utilizing skills, interests, capabilities, that are already resident in the university. For the most part in the past these had been operating as, not isolated, but, perhaps, uncoordinated programs. What we are doing here is essentially interrelating them in a structural form which would permit them to take the various capabilities they have and apply them in a coordinated way to a series of well-defined problems. Thus, each of the Institutes has a character and flavor of its own. Some are concerned with occupational health problems. Some are concerned primarily with different aspects of the body or organ system response. For example, some might relate to the effect of environmental hazard on the respiratory system. Others might be concerned with systemic handling, or detoxification of environmental agents by the liver or urinary system and the like.

Now each of these Institutes relate to one another in the sense that they do not overlap, to the best of our ability in identifying problems. At this stage of the game it is really not too much of a problem, because the field is new. The number of organizations attacking our problems are sufficiently limited that they have not begun to shove one another aside—elbow each other—in relation to the problems.

Mr. FLOOD. How many are there?

Dr. KOTIN. There are now five operational. There are four coming to the end of their planning grant.

Mr. FLOOD. Where are they?

Dr. KOTIN. The five operational ones are at New York University in New York; Harvard University in Boston; the University of Cincinnati; the University of Oregon, and Washington University in St. Louis. Those are the operational ones.

Mr. FLOOD. How did they get there?

Dr. KOTIN. They got there on the basis of design. A profiling of the resources in environmental health was undertaken by the group of people then charged with the responsibility for this program. It was identified, for instance, that for an approach at the fundamental level of interaction for the various environmental systems, aquatic, the dietary, the atmospheric—Washington University is an example of a pure denotation of research concerned with the interaction of all these environmental areas.

In a more limited area the one at Harvard University is concerned with the response to environmental agents that primarily enter the host through the respiratory system. There, because the Institute is in the school of public health, it has the added dimensions of engineering skills, epidemiologic and biometric skills, and so forth.

The University of Cincinnati with the Kettering Laboratory has as its primary focus occupational health.

While the skills and talents obviously will overlap, the problems they are attacking and their major identification characteristics are, in large measure, mutually exclusive—perhaps that is overstating it—but they are separate and identifiable.

The one in Oregon is concerned with the unique opportunity provided by the University of Oregon to study aquatic and marine environments, both fresh water and salt water. They are close by. It is also concerned with the urban and rural, because of the great forests they have, with great cities, in many instances sitting in the forests—thus, environmental interactions and their effect on the host can be studied.

Mr. FLOOD. What do the universities chip in?

Dr. KOTIN. They are supported mostly by grants, so their chipping in is in direct proportion to the general requirement of the NIH, Division of Research Grants.

Mr. FLOOD. What do you have in your budget this year and next year for all of them?

Dr. KOTIN. $3 million for Environmental Health Institutes in 1969.

Mr. FLOOD. Is that a lot?

Dr. KOTIN. It is inadequate in terms of the national need. We feel that it is adequate in the sense that the problems we are attacking in these Institutes are of a profound nature; and to insure the necessary stability for these programs, commitments must be made for a long term. The pioneering work—and I use the word advisedly—that has to be done in even developing technologies is such that we prefer to move slowly. Once a commitment is made, it is almost impossible to judge what your batting average is until 2 or 3 years have elapsed. So, we would rather move slowly and perhaps be .300 hitters than move in too rapidly and get sent back to the minors.

Mr. FLOOD. What are you doing to combat that dramatic, startling rise in the incidence of emphysema and chronic bronchitis?

I come from the hard-coal fields. This has nothing to do directly with the question, but we have what we call anthracosilicosis, and miner's asthma. I often see a boy who went to high school with me who lived down the street a couple of blocks. We might go to a wake when somebody dies in our neighborhood. We have all nationalities in that country. I'll see one of these fellows who worked in the mines and he'll look 20 years older than I do. He has anthracosilicosis, miner's asthma. Back to the question. What are you doing about emphysema and chronic bronchitis? This is not miner's asthma or anthracosilicosis, but it makes me think of it because I see these fellows every weekend.

Dr. KOTIN. I think your concern is well merited.

Mr. FLOOD. I used the word dramatic increase in the incidence. Isn't that so? Isn't it dramatic?

Dr. KOTIN. It is dramatic. I think a significant portion of the increase in the incidence is probably more related to general environmental contamination than to occupational exposure. Up until perhaps 25 years ago, unequivocally, chronic broncitis and anthracosilicosis were primarily occupational diseases.

Mr. FLOOD. Anthracosilicosis is occupational.

Dr. KOTIN. That is true, but we are beginning to find that emphysema and bronchitis particularly are diseases that are becoming hallmarks of the mid-20th century and there are many explanations for this, and these are the things we are concerned with.

We know, for instance, that people are living longer and this is a factor. We know people are recovering from pulmonary diseases that permanently damage the lung. A half century ago these diseases had high mortality rates. We have an increase in partially respiratory-deficient people who had a high early mortality rate prior to the days of effective treatment. These people are now coming of age and developing emphysema and bronchitis. We know that our cities contain a broad spectrum of chemical agents that can cause and accelerate these diseases.

Mr. FLOOD. But what are you doing about it?

Dr. KOTIN. We are taking two approaches; one is we are studying the target: the lung. It is perfectly obvious that all the people exposed to a high-risk environment do not develop the disease.

Mr. FLOOD. Why?

Dr. KOTIN. This is a good question. We would like to get some of the answers.

Mr. FLOOD. That is why I asked it.

Dr. KOTIN. We are attempting first to see whether there are measurable and definable biochemical differences between these people. For instance, we know certain enzymes in the lung are integral to the maintenance of effective secretion of pulmonary surfactant—the chemical substance lining the air spaces.

Mr. FLOOD. Is there a question of sex involved, here?

Dr. KOTIN. I do not think there is any question about that. It would appear degenerative diseases in general effect men more than women.

Mr. FLOOD. This is a degenerative disease?

Dr. KOSTIN. Yes; degenerative in the anatomic and biological sense and not sociological.

Mr. FLOOD. Do you have something specific in mind when you say degenerative, or is it a catchall phrase?

Dr. KOTIN. I think it is a very specific—I am a pathologist and I am used to looking at tissues and organs and I think there is a very specific constellation of patterns under a microscope which I would call degenerative as distinguished from inflammatory, or neoplastic, so it is not really a catchall, it is quite a precise term in the lexicon of the pathologist. It is degenerative in the sense that the elastic tissue responsible for the contractility of the lung has undergone degeneration.

Mr. FLOOD. You were telling me what you were doing.

Dr. KOTIN. What we are trying to do, first, is to see what the physiological parameters are that provide resistance to the developments of these diseases in some people; and then, whether we can buffer and protect the susceptible through what we learn from the resistant.

Mr. FLOOD. What is the difference between emphysema and chronic bronchitis? How are they different?

Dr. KOTIN. Emphysema is a disease in which the air spaces which are divided by elastic membranes——

Mr. FLOOD. Air spaces where?

Dr. KOTIN. In the lung. And the elastic membranes become destroyed so that you get progressively larger coalesced areas of air space.

And incidental to the destruction of these elastic membranes, the gas exchange apparatus sitting on these elastic membranes is destroyed as well, so respiratory efficiency is significantly reduced.

In chronic bronchitis you have a disease which is characteristic initially by a massive hypersecretion of mucous from the glands around the lining of the lung as well as the cells lining the lung.

This extensive secretion is responsible for the picture of miner's asthma that you describe. If this goes on long enough, the diminishing ability of the lung to recover from this prolonged insult of the hypersecretion, as well as the agent causing the hypersecretion, results in the cell death of much of the lung tissue. Lung tissue in turn, is replaced by fibrous tissue, so that chronic bronchitis, over the long haul, is characterized by a fibrous replacement of much of the functional portion of the lung—in contrast to emphysema, where you actually have loss of tissue and a coalescence of these air spaces.

### RELATIONSHIP TO AIR POLLUTION CONTROL DIVISION

Mr. FLOOD. Does the research done in your shop overlap with that done in the Division of Air Pollution Control?

Dr. KOTIN. We complement each other, I think, would be a bit more precise, if I may say so.

Dr. Middleton has a series of current problems and current needs. Among these are the information to establish standards. Now these standards, which are just numbers, are based on criteria, which essentially are facts. These criteria are obtained from both combined experimental studies and epidemiological studies.

It is our responsibility to provide the criteria so that, rather than a "seat of the pants" guess as to how many units of $x$ is allowable, there will be a rational basis for assuming that five molecules of something is hazardous, whereas three is tolerable in the environment. It is Dr. Middleton's job to say five or three. It is our job to provide him with the facts upon which to base, as intelligently and as correctly as possible, his choice of five or three.

ENVIRONMENTAL HEALTH CENTER

Mr. FLOOD. What was the first appropriation that you had to start planning the Envioronmental Health Center?

Mr. KINGMAN. Sir, may I put that in a proper time frame? Last year, Mr. Chairman, was the first year that Dr. Kotin appeared before this committee. The planning money was made available some years prior to that.

Mr. FLOOD. What was the first amount?

Mr. KINGMAN. The first amount was $785,000, which was made available in 1961.

Mr. FLOOD. What is the status of the planning on that facility, now?

Dr. KOTIN. We currently occupy some 25,000 square feet. We are going to acquire an additional 10,000 square feet through the relocation of the National Environmental Health Sciences.

The master site plan for the 509 acres which was deeded to the Department in September 1967 and the program of requirements for the first phase of construction should be finished by January 1969. We project that the architect-engineer's contract will be awarded in April 1969. The design for the permanent facility should be completed by May 1971, and construction, we hope will be completed by August 1974.

By February 1969 we are scheduled to occupy 11,212 square feet, acquired through the relocation of the National Center for Health Statistics plus an additional 18,000 square feet of office and warehouse space. Phase II, a construction project addition to our own interim space, was authorized at the time of the establishment of the National Center. The engineering and the design for this extra 30,000 square feet—the phase II in our rented facilities as distinguished from

the permanent facility—has progressed to the point where now an architect-engineer has been hired and we plan on being in there about January 1970.

Mr. FLOOD. You are a new man and it is no reflection on you, Doctor, but the committee has been here a long time. We go on like Tennyson's brook, you see. We have been at this for 7 years with this environmental health center. Nothing happend. Why? Who has been dragging their feet over there?

Dr. KOTIN. If I may suggest, what looks like a complete dragging of feet has really not been a standstill—and as you point out, I do not feel I am defending anything I have done.

Mr. FLOOD. That is correct.

Dr. KOTIN. As measured in terms of bricks and cement, things appear static. It really has not been a dragging of feet in the important areas of program evolution. The environmental health program is pioneering in the strictest sense of the term. It is concerned with the effects of long-term low-level exposure in the laboratory and the utilization of study populations as the other side of a coin to the experimental approach. The inevitable commitment to any area of research must frequently be considered almost in terms of decades. It requires as much time as has been spent, which is infinitely more time than an experiment where you are going to measure the toxicological effect of an agent and get an answer on the difference between 20-days survival and 40-days survival.

We are concerned with survival measurable in terms of segments of the life span of man and the animal. This takes planning; and, I submit, long before I was associated with the Division the very nature of on-going work in chronic toxicology was providing a background for this.

The housing of the program in the Bureau of State Services prior to its move to NIH provided some indispensible ingredients that we do not have to get now. When it was in the Bureau of State Services, it provided a bridge to those responsible for Bureau activities at the level of monitoring, standards, enforcement, and regulation. There has not really been a total loss of time. I speak now in the sense of being responsible for the scientific program, not in terms of other considerations.

Mr. FLOOD. A complete history of this National Center proposal has been prepared at the committee's request. We will place it in the record at this point.

(The matter referred to follows:)

# HISTORY AND STATUS OF THE NATIONAL ENVIRONMENTAL HEALTH SCIENCES CENTER

## Introduction

In the interval since the end of World War II there has developed a growing national awareness of the enormous impact which man is having on his physical and social environment. As has been pointed out in numerous national studies and in the scientific literature, man is now capable of adversely affecting his environment in a manner that increases its hazard to health.

The growth in American population projected over the next twenty years and the increasing complexity of American society makes imperative immediate effort directed to the procurement of answers to fundamental questions of environment and health which will not only affect our lives but those of our children in the years to come. There is general recognition that past efforts have been slow in developing, current efforts are inadequate, and that further delay will inevitably mortgage the well-being of coming generations.

The Division of Environmental Health Sciences, with its intramural program the National Environmental Health Sciences Center, was established in response to both the threat and the challenge of the future. Its research programs have as their goal the advancement of fundamental knowledge and the development of a scientific base which will serve to provide answers to questions which man's interaction with his environment will inevitably generate in the coming decades.

## History

The National Environmental Health Sciences Center grew out of the efforts and concerns of many different groups and individuals in the ten year period beginning in 1958.

One of the first expressions of concern regarding the possible interrelatedness of man's health and the quality of his environment was contained in the Bayne-Jones Report in June 1958 to the Department of Health, Education, and Welfare entitled: "The Advancement of Medical Research and Education." The report supported continuing and expanding research related to numerous environmental factors.

In June 1960 a study group on mission and organization of the Public Health Service reported to the Surgeon General that, among other areas of concern, environmental health problems could be identified as one of two broad areas that would require increased public and private effort in coming years. The group's final report stated: "The lag in adjustment of environmental factors to limits of human tolerance is particularly striking." The report also predicted that a central laboratory facility would be needed for basic research in environmental health.

In 1961 the Public Health Service proposed the establishment of an environmental health center with facilities for research, technical assistance, and training in the Washington, D. C. area. The Service also declared that the major obstacle in meeting environmental health problems was lack of knowledge and that the Nation's greatest need was and would continue to be research, both fundamental and developmental.

In November 1961, the Committee on Environmental Health Problems, headed by Dr. Paul Gross, recommended to the Public Health Service that a national center be established that would undertake integrated research as well as other activities related to environmental health. The Gross Report served as a catalyst in drawing together highly divergent opinions and concepts of how to undertake the development of a fundamental and basic research program in environmental health.

In September 1964 the Congress authorized funds for the planning of a central research facility; but at the same time declared that it should be located more than 50 miles from the District of Columbia.

A site selection committee considered a number of possible locations throughout the United States. The committee's deliberations led to the selection of the Raleigh-Durham-Chapel Hill area -- where the three universities, North Carolina State, Duke, and the University of North Carolina; the State government; and private industry had developed the Research Triangle Park, located equidistant from the three cities of Raleigh, Durham, and Chapel Hill.

In April 1965, a small group drawn from the National Environmental Health Advisory Committee and led by Detlev W. Bronk, President of the Rockefeller Institute, recommended to the Surgeon General that the Center be operated not by contract mechanisms as had been suggested by some, but directly by the Public Health Service. The Bronk group also proposed that the Center's activities be directed by an outstanding scientist-administrator, and that appropriate advisory bodies be appointed to advise the Director on program plans and priorities.

As part of the general reorganization of the Public Health Service the Division of Environmental Health Sciences was established as part of the National Institutes of Health on November 1, 1966; and Dr. Paul Kotin was appointed Director.

Throughout the remainder of Fiscal Year 1967 the Division engaged in vigorous recruitment efforts as well as planning for new research facilities. On January 1, 1967 the Division had 31 employees; on June 30, 1967 a total of 66; and 130 as of January 31, 1968. Thus, to date the Center has been extremely successful in attracting scientists as well as technical and administrative support staff to the Research Triangle Park location.

The Bureau of the Budget has just approved the use of $225,000 for master site planning of the Environmental Health Science Center at the above location.

The progress through the last year is encouraging in terms of the development of a vital, active research organization and it is to be hoped that the Center, as presently developed, will serve as a powerful attraction to scientists concerned with research of relevance to environmental health.

Current Status

The National Environmental Health Sciences Center was created for the purpose of investigating at the fundamental level the long-term and subtle effects of environmental agents potentially hazardous to man. These studies will be directed to the development of a base for establishing standards and devising remedial measures. The increasing complexity of our environment makes it imperative to view the problems of environmental hazards from the vantage point of total health effects. It is this information that is necessary before an effective foundation can be constructed so as to assure protection of exposed populations. Complementing the experimental laboratory studies, the Center will engage in long-term epidemiological studies of populations with unusual environmental experiences or unique morbidity and mortality experiences. The third aspect of the Center's projected program will include a clinical research program which will have as its primary objective the study of individuals and samples from defined population groups for the purpose of determining the effects of exposure to low concentrations of known or suspect environmental toxic agents over long periods of time. These studies will seek to identify the basis for variations in response to environmental insults and assess on an ongoing basis the compatibility of experimental laboratory data with human data. It is hoped that this approach will assure maximum extrapolation of laboratory findings as well as provide important principles and generalizations to permit the development of effective guidelines with which to judge the myriad new agents constantly entering our environment.

In summary, the Center will provide a central facility for research on the total health effects of physical, chemical and other environmental factors to which the American people are exposed.

The function of the Center is to identify harmful agents in the environment, discover the mechanisms by which they affect an individual's health, and develop data on the effects of chronic exposure, thereby providing a scientific base upon which control measures can be developed. The seven classes of environmental agents on which we are now initiating research projects are natural products, metal compounds, hydrocarbon reaction products, tobacco smoke constituents, polymer dusts, pesticides, and pesticide synergists.

In its cell biology branch the Center is currently involved in studies of natural products and with enzyme induction and metabolism of toxicants. The work in natural products is concerned primarily with toxins produced by fungi on foodstuffs.

Pilot studies with selected chemicals are being initiated to establish a model system for studying the effects of toxicants on the structure, function and biogenesis of mitochondria, which play a key role as regulators of the metabolism of cells. Thus, chemical agents that interfere with mitochondrial activity may also affect cellular growth and function.

Cultures of mammalian cells have been established for the study of enzyme induction by certain chemicals. Because these processes are part of the primary defense mechanism against environmental pollutants, understanding of the induction process per se and of the factors which contribute to its operation becomes increasingly important as the body load of foreign compounds from environmental sources increases.

The analytical and synthetic chemistry branch of the Center augment the functional programs of the Center by developing new and improved analytical

techniques for determining micro qualitative and quantitative determination of many chemicals. They aid in determining purity and stability of chemicals, identifies trace metals and other environmental substances, such as flavors, food additives, or pesticides. Studies are also being carried out on the degradation products of some of these chemicals.

The Center's animals science and technology branch provides, maintains, and monitors all animals used in the Center research programs. The branch is also currently engaged in several research programs both on its own and in conjunction with the chemistry and cell biology branches. Several pesticides and other environmental chemicals are being studied in an effort to determine their effect on the enhancement or suppression of immune response.

The investigations of the pharmacology and toxicology branch are concerned with the assessment of the significance of initial interactions between environmental agents and living systems in disease. In addition these investigations will attempt to characterize the mechanisms of effect for the purpose of both seeking practical means of control and gaining sufficient understanding to permit the prediction of those agents or classes of agents and their possible effects that may be harmful.

The program is concerned with the chronic, the less obvious, and unexpected effects, as well as the acute and the more obvious. By their nature, acute effects are relatively easy to detect and to associate with a causative agent. Chronic effects are not only more difficult to associate with a specific causative agent, but they are also readily modified by secondary interactions. Time, in the chronic effect, introduces the potentiality of greater variation in the type of manifest response.

In contrast with many studies of the occupational environment, the emphasis in the program of the Occupational Studies Group is placed on the identification

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of disease states in man which appear many years after exposure to causative agents. While evidence accumulated to date indicates that many industrial processes may be implicated as the cause of disease, insufficient research has been done in this area due to lack of data resources, unavailability of scientific and administrative support, and limited cooperation of industry in undertaking such studies. The growth in number and reliability of data sources for identification and follow-up of exposed populations, as well as a spirit of willingness and cooperation on the part of industry, have now made it feasible to initiate an occupational studies program. The current research program includes the study of uranium miners and millers, steelworkers, coke-oven workers, hard rock miners, chromate painters, smelter workers, and workers exposed to cutting oils.

The office of scientific information maintains intimate contact with program planning and current operations in the operational environmental health regulatory and control programs of the Service. In addition, this office is developing a system of scientific intelligence designed to identify and strengthen sources of information on the existence of environmental hazards, warranting intensive study or research. This office also provides scientific reference services for the intramural scientists.

Conclusion

In sum, this is the National Environmental Health Sciences Center today. Established in response to a public recognition of critical national need; its programs are aimed at the measurement of long-term, low-level exposure to environmental hazard in terms of its effect upon human health. The Center is now prepared to develop significant and urgently needed investigations. The

rate at which the Center is able to accomplish the development of its research programs is a matter for public policy determination. The scientific need for extended research in this area is persuasive.

Our history is replete with examples of thoughtless waste of our natural resources and wealth. The continuing technological development of the United States without concomitant understanding of the negative as well as beneficial impact of that development threatens our nation with health hazards as serious as our past waste of natural resources.

The lessons of history are stark and compelling. We must strive to understand the health significance of the environmental changes which we are affecting with such increasingly facility. The National Environmental Health Sciences Center as one major national resource is now prepared to undertake investigations aimed at increasing that understanding.

COMPOSITION OF DIVISION PERSONNEL

Mr. NATCHER. Dr. Kotin, how many people do you have in your division at this time?

Dr. KOTIN. 131, sir.

Mr. NATCHER. Of this number, how many are research scientists?

Dr. KOTIN. We have 46 professionals, of whom 42 are scientists.

Mr. NATCHER. Would you supply this committee with the names of your top level research personnel and tell us what their last previous employment was and in what capacity they were employed, Dr. Kotin, at this point in the record?

Dr. KOTIN. Yes.

(The information requested follows:)

DIVISION OF ENVIRONMENTAL HEALTH SCIENCES—SENIOR SCIENTIFIC STAFF

| Name | Title | Last employer |
|---|---|---|
| Dr. Otto Bessey | Scientist administrator | Bureau of Disease Prevention and Environmental Control, National Center for Urban and Industrial Health, physical science administrator. |
| Dr. Lawrence Fishbein | Chief, analytical and synthetic chemistry branch. | Bionetics Research Laboratory, Falls Church, Va., principal investigator, pesticide research program. |
| Dr. Paul Kotin | Director | National Institutes of Health, National Cancer Institute, Scientific Director, Etiology. |
| Dr. Douglas H. K. Lee | Associate Director for Scientific Information. | Bureau of State Services, Chief, Occupational Health Research and Training Facility. |
| Dr. William Lloyd | Head, occupational studies unit | National I stitutes of Health, National Cancer Institute, statistician (health), occupational health program. |
| Dr. Frank Lundin | Senior epidemiologist | National Institutes of Health, National Cancer Institute, Head, Special Studies Section. |
| Dr. Robert Owens | Chief, cell biology branch | Bureau of State Services, Deputy Director, Laboratory of Pesticides Research, and Chief, Chemistry Section. |
| Dr. Hans L. Falk | Associate Director for Laboratory Research (currently performing duties of both this and previous position). | National Institutes of Health, National Cancer Institute, Associate Scientific Director for Carcinogenesis. |
| Dr. William W. Payne | Deputy Director | National Institutes of Health, National Cancer Institute, Deputy Scientific Director for Etiology. |
| Dr. Herbert Posner | Head, Section on Growth and Development. | National Institutes of Health, National Institute of Dental Research, research pharmacologist. |
| Dr. Lawrence Tuttle | Staff assistant to Director | Tulane University, professor of radiology and head, division of environmental health, delta primate center. |

LABORATORY AND CLINICAL RESEARCH

Mr. NATCHER. I see you requested an increase of $788,500 for laboratory and clinical research to be done within your own laboratories and you are estimating an increase of 54 positions for this activity. At the same time you are budgeting almost no increase for research grants. Aren't you building up your own organization at the expense of developing skilled people in the universities and outside institutions, Dr. Kotin?

Dr. KOTIN. I don't believe so, sir. One of the things I have tried to emphasize and perhaps did not do it too well is that both the institute centers and research grants represent part of a composite. The National Center is the hub of a nationwide coordinated, integrated attack on problems of environmental health. From this hub there radiate activities in non-Federal facilities supported by diverse means. At this stage of the game, we feel that if indeed we are going to be the focal point and assure unnecessary duplication, and further be able to attack problems which suddenly present themselves, of a fire brigade nature perhaps, we must develop the in-house competency which can relate to, collaborate with, and capitalize on the extramural activities.

So this is a transient acceleration in our growth. Your observation is correct, but I think it is just part of the evolution of the National Center.

Certainly at no time—and I recall this from my testimony last year—is it ever envisioned that the National Center, per se, will have been or will ever be anything other than a very small component of the total national effort in environmental health supported with Environmental Health Division funds.

### REVIEW AND APPROVAL OF GRANTS

Mr. NATCHER. Now, Dr. Kotin, although you are not planning to increase the level of funding for research grants, you are asking for additional funds for review and approval of grants. Why do you need more people and more money for a review of grants, Dr. Kotin?

Mr. KINGMAN. I wonder if I might speak to this: The workload of our extramural staff is a function of the grants received and reviewed rather than the number of grants awarded. Moreover, one of our major responsibilities is to insure the most effective use of our grant resources. It is only through having an adequate number of scientific and management personnel that we can insure that, on the one hand, the grants which Dr. Kotin approves are of high scientific quality, and, on the other hand, that the grantee institutions possess the management capability to administer the expenditure of Federal funds wisely and effectively.

Dr. KOTIN. In addition to competency, availability of resources, and all the other things that go to make a grant supportable, we are very much concerned with relevance. In fact, it is the indispensable ingredient. The relevance of the grant to our program, and to the broader programs as evolved in the hub—with consultation, of course, of our advisory committees and the like is maximal. This requires scientific judgment by the review and approval staff on yet one additional dimension: relevance.

This requires scientists who, in addition to judging the caliber of work, are fully aware of the in-house program, its projections, its needs, and also the long-term requirements for nationwide activity. They have to be able to identify not only good people, but good people who are working in an area that is relevant to the mission of the Division.

### CENTRAL PROGRAM MANAGEMENT STAFF

Mr. NATCHER. I see that between review and approval of grants, and program direction, Dr. Kotin, you plan to add 50 people and spend around $850,000 in fiscal year 1969. Isn't your budget rather topheavy with administrative expense?

Mr. KINGMAN. Sir, I beg to take exception. We are not planning to add 50 people in those two activities combined.

Mr. NATCHER. How many are you going to add?

Mr. KINGMAN. Our total budget proposal requests an additional seven for those two activities.

Mr. NATCHER. Instead of 50?

Mr. KINGMAN. Yes, sir.

Mr. NATCHER. Do you show 50 anywhere in the justifications?

Mr. KINGMAN. We show a total increase of 54 positions, in our laboratory research.

Mr. NATCHER. Do you set up a separate figure of 50 anywhere in the justifications other than the 54 that we have just discussed?

Mr. KINGMAN. If I can have the opportunity to review this when I get back to my office, I would say "No," sir.

Mr. NATCHER. If you find that is incorrect, you can change the transcript accordingly.

Mr. KINGMAN. Yes, sir.

(Information requested follows:)

CENTRAL PROGRAM MANAGEMENT STAFF

In 1969 there will be a total of 50 people in review and approval and program direction combined. However, there is only a seven-position increase for these two activities in 1969.

The Division of Environmental Health Sciences constitutes the first major component of the National Institutes of Health to be located away from the Bethesda headquarters. It is an organization having a broad range of program responsibilities for which major growth is planned. Thus, it has been necessary to develop a staff competent to carry out the Division's wide range of program planning, management, and administrative responsibilities, including those of the extramural staff located in Bethesda, Md.

In summary, in its first 2 years the Division has developed its central staff very rapidly. Now that these staffs have been assembled, it is planned to add individuals only in response to the challenge of newly assigned responsibilities or in response to increased workload. The current level of central staffing is comparable to those of other organizations having a similar breadth of responsibility.

REVIEW AND APPROVAL OF GRANTS

Mr. NATCHER. Now, Dr. Kotin, in last year's request, you estimated spending $356,000 for review and approval of grants, is that correct? Do you agree on that figure?

Mr. KINGMAN. Yes, sir.

Mr. NATCHER. Now, in spite of the $3 million reduction and the fact that you awarded much less research grant money than you planned, you estimate that you will have spent $420,000 on review and approval of grants in 1968. Now, do you gentlemen agree on those figures?

Dr. KOTIN. Yes, sir.

Mr. KINGMAN. Yes, sir.

Mr. NATCHER. Now as to the $420,000; how do you explain that, Dr. Kotin?

Dr. KOTIN. I can only answer it in the sense that the grants program is essentially a scientific program, requiring a larger proportion, I believe—and I can't verify this; I haven't checked with the other Institutes—a larger proportion of scientists sufficiently senior to arrive at major program judgments. In addition to that, the missionary work that we have to do in the establishment of the environmental health institutes in the universities requires almost getting down to the protocol level to assure that the mission of the Division, the needs of the Division, are met by these activities. They are almost quasi—and maybe this is a bad thing to say—they are almost quasi-in-house, although supported by the grants mechanism, because they are concerned with clearly defined end points evolved by the Division in consultation with its advisory committees. This, I think, is perhaps a little different than the traditional approach to grants. I repeat the word

again. We are almost compulsively concerned with relevance of all dollars in the Division budget to its mission. In order to translate that concern into action, adequate staffing is mandatory.

TOBACCO AND HEALTH

Mr. NATCHER. Now, Dr. Kotin, last year you told the committee that you planned to spend $480,000 in the area of tobacco and health. Will you tell me now how much you estimate you will have spent in this area by the end of the fiscal year 1968?

Dr. KOTIN. $247,000.

Mr. NATCHER. What projects are presently underway in your laboratory, Dr. Kotin, having to do with tobacco and health?

Dr. KOTIN. There are three major activities going on. We are the recipient of all the cigarettes that the Federal Trade Commission does not use in their quantification of tar and nicotine. Because they have to buy a large number for random samples, and by means of the very elegant technique of emission spectroscopy we are doing trace metal analyses on a very large sample of cigarettes as a baseline for other ongoing studies; we are concerned with the toxicological effects of disturbances in trace-metal balance in the intact host and in cell systems.

Another activity with which we are concerned is the hazard that may exist incidental to fungal contamination of tobaccos and particularly cigarette tobacco which, by virtue of storage for a long period of time, provides a fine culture media.

We are asking three questions: Are these contaminants delivered into the smoke?

Mr. NATCHER. Right at that point, Dr. Kotin, how much of your money are you allocating to this particular fungus study? Can you give the committee some idea? Just approximately.

Dr. KOTIN. By the end of the year it would be about $75,000.

NATIONAL TOBACCO RESEARCH LABORATORY AT UNIVERSITY OF KENTUCKY

Mr. NATCHER. Do you know of the work now being conducted in the National Tobacco Research Laboratory at the University of Kentucky?

Dr. KOTIN. Yes, sir.

Mr. NATCHER. Do you know the type of research that they are carrying on out there, Doctor?

Dr. KOTIN. Yes, sir.

Mr. NATCHER. Isn't this a complete duplication?

Dr. KOTIN. Not at all in the sense that we are aware of their approach. We are much more concerned with the basic mechanisms of fungal persistence. They are concerned primarily with the—you can correct me on this, perhaps—their activity is not concerned with profiling tobacco. They do not have the large samples of tobacco that we have. We, in essence, are using the samples of tobacco we get through the Agricultural Experimental Station. We are under process of negotiating a contract which will be concerned with determining if there is any way that you can preclude the development of this mold or create an environment that would be unfavorable to the development of this mold in tobacco. Our approach there is essentially to work out the mechanism to determine the presence of the hazard

with a view to identifying techniques for buffering against, or protecting against the hazard. This is not being done, as I recall, in the University of Kentucky.

Mr. NATCHER. Now, Dr. Kotin, what other programs do you have underway in the field we are talking about?

Dr. KOTIN. We are not doing anything yet except evolving the techniques for the other side of the coin. Pesticide residues in tobacco; we are concerned with the tobacco being a crop, as with all other crops, edible or otherwise. Is there a hazard in the residues of pesticides which remain at the time the consumer gets the product?

Mr. NATCHER. Right at that point, Doctor, do you know whether or not this type of research is under way at the University of Kentucky as far as pesticides are concerned?

Have you ever checked, Doctor, to find out just what they are doing down there?

Dr. KOTIN. Yes, sir. I get their quarterly and semiannual reports through the Department of Agriculture. I am aware of the $1.5 million appropriation they received and have been receiving for several years. The Surgeon General was requested by the Secretary of Agriculture to designate a responsible person to represent the Department of Health, Education, and Welfare, and the Surgeon General. Terry, at that time, designated me. I have been to Lexington. I would say within the last year no less than four scientists from the University of Kentucky program have visited the National Environmental Health Sciences Center. Dr. Burdick and Dr. Stedman, and Dr. Woodward and Dr. Senci from the Department of Agriculture, have been to the National Center all within the last 2 months. In addition, several discussions have been held with Dr. Hoover of the Department of Agriculture.

Mr. NATCHER. You were down there, Doctor. What did you find out about research in regard to pesticides used in tobacco?

Dr. KOTIN. At the University of Kentucky, at that time there was no mention of it in the presentation that was made that I attended.

Mr. NATCHER. The fact that it wasn't mentioned in the presentation made during your presence doesn't mean it is not underway, does it?

Dr. KOTIN. In the agronomy school there is a large amount of activity going on in the field of pesticides.

### SIGNIFICANCE OF TOBACCO INDUSTRY FOR THE ECONOMY

Mr. NATCHER. You know, Doctor, I serve on the Subcommittee on Agriculture Appropriations and I have for 14 years. The tobacco industry is a $10 billion industry. In 22 States 700,000 families are involved in raising tobacco. My home State of Kentucky produces more tobacco than any other three States in the United States, with the exception of North Carolina. Beginning in 1958, Dr. Kotin, on the Subcommittee on Agricultural Appropriations, I informed the Department of Agriculture that we needed more research in regard to tobacco. If tobacco is harmful to the health of the people in this country, we want to know about it.

Finally I got the Department of Agriculture and the House of Representatives to go along on an increase of about $250,000. We

raised that amount up to $1,500,000 which, as you know, is simply a drop in the bucket. When you consider all this money that you have in grants, in the Department of Health, Education, and Welfare—billions of dollars—$1,500,000 is just a drop in the bucket. Do you agree to that, Doctor?

Dr. KOTIN. It is certainly a comparatively small amount.

Mr. NATCHER. When Dr. Terry appeared before the Committee on Agriculture after releasing the report on smoking and health, he was asked the question: Is there need at this time for additional research in tobacco? You can go back and check the hearings. He said "Absolutely."

"We need more research now."

That was within a matter of 2 weeks after the report was released.

Now, Dr. Kotin, in the State of my colleague, Mr. Hull here of Missouri, and in my home State of Kentucky, all we are asking you and your associates to do is not to destroy a $10 billion industry until we have a chance to do something about it.

This is an important matter to a lot of people. We started long before you did, Doctor, and we started in a small way, and we are sincere, and we are honest in our efforts. We don't intend for you or anybody else to destroy the tobacco program. That is the reason that I am asking you these questions.

We have made a sincere effort and we are going to continue our efforts. My people today, Doctor, in the State of Kentucky believe that if tobacco is harmful to the health of our people, we must do something about it. But we want to stop all this guessing, Doctor. That is all we ask. Let's just stop the guessing.

That is the reason I am propounding these questions to you, Doctor, and I am going to propound them to you as long as I serve on this committee. I say that to you frankly.

Now, all we are trying to do is to make a good, honest effort to find out what the trouble is and, if it is caused by tobacco, we want to do something about it. That applies to you, Doctor, and it applies to all of your associates. That is our feeling about this matter, Doctor.

Dr. KOTIN. I don't think we are far apart. When the Scientific Advisory Board to the tobacco industry was established, I was invited as a charter member and served for 10 years on the committee. I obviously felt that it was a situation that merited scientific attention and I assumed I was invited because of interest in the problem. However, had I felt the situation was all locked up and all the facts were known, I never would have accepted membership on the committee. I serve on the American Medical Association Committee on Smoking and Health, on their advisory committee as further evidence of my conviction that additional information is necessary. I know the concept of a less hazardous cigarette is something that I have contributed to, in part, in its evolution, and in terms of conviction because, again, life is too short to spin wheels on things which there is little feasibility of achieving.

I don't think we are nearly as far apart as would appear.

Mr. Natcher.

I agree with my chairman that you have great ability and I hope that we understand each other a little better.

TOBACCO AND HEALTH RESEARCH IN 1969

How much do you expect to appropriate to tobacco and health research in fiscal year 1969, Doctor?

Dr. KOTIN. In terms of clearly definable dollars in the Division, $307,000, which includes $175,000 in our Institute grants. Consistent with the availability of resources we are going ahead with the impetus that the problem merits. We can attack it on many fronts, in a manner that was impossible, technologically, if you will, only 5 years ago. Things like gas chromatography, nuclear magnetic resonance, and electron spin resonance are analytical tools that are just beginning to give us the wherewithal to operate at the micro level that is necessary. After all a brick doesn't hit a cell; it is a tiny segment of silica in the brick that does. This is a poor analogy, but nevertheless, I think you know what I am trying to say: we must have tools to operate at minute levels of interaction.

What we have done is, more or less operate in a coordinated fashion. Dr. Endicott, Dr. Frederickson, and myself have met; and essentially Dr. Endicott's budget reflects a significant amount of money that will be spent under the aegis, if you will, of the coordinated program of the Division and those Institutes. So that while we show $307,000, I would suspect that it would be much more than that. In this sense we are now capable of doing things that we just weren't able to do—one doesn't have much from a professional career except his work, and I have worked in the field of tobacco and health now for better than a decade. Things that were undreamable 5 years ago are now capable of being done with instrumentation. We are going to spend about $350,000 to $400,000 I would say, sir.

PESTICIDE RESEARCH

Mr. NATCHER. Now, Dr. Kotin, how much will you spend in fiscal year 1968 for pesticide research?

Dr. KOTIN. Twenty percent of our in-house budget is devoted to pesticides and pesticide synergists. Really, a significant portion of that pesticide budget is tobacco research as well. The techniques being used by people geared in pesticide analysis apply whether they are dealing with peanuts, cotton, or other substances. They are also using them in studying tobacco as well.

Mr. KINGMAN. Pesticide research constitutes the largest single portion of our extramural activity. We currently have something of the order of $2 million in our research grants program devoted to pesticides research.

HEAVY METALS AND TRACE ELEMENTS RESEARCH

Mr. NATCHER. Will you give me some information, Dr. Kotin, in regard, first, to heavy metals and trace elements, as to what you are doing on this particular program at this time and, in addition, how much you estimate will be expended in 1969?

Dr. KOTIN. The purpose of the research in heavy metals and trace elements is to study the chemistry and biology of the interaction of selected elements with cells and tissues. Studies on the biologically essential trace elements including zinc, copper, manganese, and iron

compounds are being initiated. We wish to examine them as they occur in inorganic compounds or as metalloproteins using simple enzyme systems, tissue culture systems, and the intact host for the purpose of determining their role in the host response to noxious agents in the environment. The effects of alterations in trace metals on enzyme formation and functions are being studied in mammalian cells.

In addition, such heavy metals as lead, nickel, and chromium are demonstrated environmental toxic substances; and our research is aimed at determining whether a threshold for their toxicity exists, whether they exert a long-term adverse effect incidental to their storage in tissues, and finally whether it is possible to protect tissues against their effect. Lead has adverse effects on the urinary system, nervous systems, and the red blood cells. Lead acetate can produce cancer in rodents. Human exposure to chromates is associated with an increased risk to lung cancer, and nickel exposure carries with it an increased risk to cancer of the sinuses, lungs as well as other chronic effects such as perforation of the nasal septa. As with all of our studies, primary emphasis is being directed to low levels of exposure over long periods of time. Studies on cadmium, beryllium, boron, and titanium, though not in progress, are indicated because of their growing presence in the environment.

In 1969 we anticipate the investment of $912,000 in this area of research activity.

### RESEARCH ON MYCOTOXINS AND OTHER NATURAL TOXINS

Mr. NATCHER. Dr. Kotin, tell the committee how much you intend to expend in 1969 on mycotoxins and other natural toxins. Give us some idea as to what you have underway.

Dr. KOTIN. In the area of natural products and mycotoxins the following research is underway. The effect of the mold product aflatoxin on fertility as well as the induction of congenital malformations is being studied in experimental animals. The effect of aflatoxin and its metabolites as secreted in the milk of nursing mothers is being tested in two ways. Animals, born of mothers fed aflatoxin are being nursed by natural mothers, and newborns from mothers who have not been fed aflatoxin are being foster nursed by lactating females on aflatoxin. In addition, the milk is being examined chemically for the identification of metabolites of aflatoxin to see whether any of these are the equivalent of the parent compound in toxicity and also to determine whether any unchanged aflatoxin is secreted through the milk. The conditions favoring growth and survival of the fungi in consumer products are being investigated. The stability of the toxic products of fungi and the characteristics responsible for toxicity and carcinogenicity are being studied. The effects of exposure to low levels for long periods of time in feeding experiments are also being studied. The biochemical studies of their action include efforts to determine a threshold as well as their interaction with other toxic agents. A major portion of the studies on the physiology of mold organisms is directed to those aspects which may suggest potential control measures.

In 1969 we expect to have a program totaling $1,040,000 in this aspect of our research.

HYDROCARBON AND ITS REACTION PRODUCTS

Mr. NATCHER. Now, what about hydrocarbon and its reaction products? Tell us what you are doing in that and how much you are expending.

Dr. KOTIN. Our current investigations on hydrocarbons and hydrocarbon oxidation products include studies on chlorinated hydrocarbons used as pesticides.

Many of the flavoring agents use in consumer products are oxidation reaction products of hydrocarbons. In studies now underway, analyses are being performed to determine their presence and structure. Some of these compounds are being synthesized so that they may be used for laboratory studies on their anatomic and metabolic fate following entry into the host.

A second group of hydrocarbons with which we are concerned belongs to the polycyclic hydrocarbons, which include many compounds known to be carcinogenic. We are concerned with elucidating their mechanism of action as well as their interaction with other environmental agents. In addition, hydrocarbon reaction products are significant contributors to many of the ill effects resulting from exposure to polluted urban air. Our interests and efforts in understanding the action of these compounds are at the level of determining whether a threshold exists for their effect, the possible reversibility of their effect, and, when cirmcumstances warrant, long-term, low-level bioassay experiments to fully determine the mechanisms of hazard development.

We are currently expending approximately $2 million in this area of research.

BIOASSAY EXPERIMENTS WITH TOBACCO SMOKE

Mr. NATCHER. Dr. Kotin, are you conducting any bioassay experiments with tobacco smoke, or constituents of tobacco smoke? Describe to the committee just what you are doing along this line.

Dr. KOTIN. The Division is at present performing no in-house bioassay experiments. In collaboration with the National Cancer Institute, it is supporting such activities through the contract mechanism, and through its own grants program is supporting other research in this area. We are, however, engaged in the laboratory aspects of smoking and health including the pyrolysis of menthol as used in cigarettes for the purpose of identifying the reaction products. Studies show that menthol does not break down into any of its oxidation products.

The Division is the recipient of cigarettes from the Federal Trade Commission. These cigarettes are part of the very large sample obtained by the FTC for use in its measurement of tar and nicotine. Preparations have been completed for fundamental studies on the constituents of the non-combusted tobacco as a basis for future continuing studies on combustion and pyrolysis products. Individual constituents of cigarette smoke such as phenols and hydrocarbons are being tested in cell systems for the purpose of identifying mechanisms of toxicity.

LUNG CANCER TASK FORCE

Mr. NATCHER. The National Cancer Institute has requested an appropriation of $1.4 million toward the support of a lung cancer task force, of which you are a member.

Give the committee some idea as to the use of this money and just what is being done.

Dr. KOTIN. The lung cancer task force is concerned with initiating and supporting studies concerned with identifying environmental factors associated with increased risk to lung cancer, identifying the components of the environment responsible for this increased risk, and determining the mode of action of these agents for the purpose of providing a firm scientific base on which to suggest methods for reducing or eliminating the hazards from the environment or protecting the host against their effects. Environmental experiences associated with an increased risk to lung cancer include urban residence, cigarette smoking, and certain occupational exposures such as to chromates, nickel, coking operations, asbestos, and alpha-ray emissions as occur in uranium mines. The lung cancer task force proposes to initiate studies concerned with all of the environmental experiences associated with an increased risk to lung cancer and factors concerned with susceptibility and resistance. In addition, research aimed at facilitating early diagnosis and improved treatment is to be supported.

In implementing these activitives it has already established a subcommittee concerned with the development of a less hazardous cigarette. This subcommittee is made up of Federal and non-Federal scientists, the latter including representatives from the research laboratories of the tobacco industry. One meeting has already been held, and a 2-day meeting is scheduled for May 1 and 2. At this time a review of the current status of the problem will be completed and a series of recommendations for future efforts will be formulated. A plan of action to serve as a guideline has been evolved, utilizing a systems approach, thereby assuring the most effective utilization of funds with program review procedures and decision points identified. The Division of Environmental Health Sciences is collaborating with the National Cancer Institute and the National Heart Institute in this effort.

Mr. NATCHER. I understand the lung cancer task force has proposed the investment of some $32 million, in the next 5 years in its total assignment. Presumably a significant percentage of that sum would be devoted to the smoking aspect of its assignment. In addition, the National Cancer Institute, the National Heart Institute, the Chronic Disease Control Center, and the Surgeon General's Office are requesting funds for research relating to tobacco and health. I believe that is correct, Dr. Kotin. What is your relation to these programs? How does your Center fit into this?

Dr. KOTIN. Our efforts in this area are devoted exclusively to research for the purposes described in my answer to your earlier question on this subject and have no programmatic relation to the efforts of the National Center for Chronic Disease Control. The latter is concerned with public education and social aspects of cigarette smoking as a pattern of behavior. The Directors of the three NIH components concerned (Environmental Health, Cancer, and Heart) have met, and agreed that with the approval of Dr. Shannon, the Division of Environmental Health Sciences would assume managerial responsibility for the collaborative efforts independent of the specific funds that

may be available from each of the NIH units that have research interests and responsibilities in this area. This will insure a broadly based, coordinated effort free of unnecessary duplication and, furthermore, will permit immediate implementation of the results of research. Scientists from the three NIH components will meet at regular intervals for the purpose of review and measurement of progress. The lung cancer task force will be included as one activity within this coordinated approach.

ASBESTOS HAZARD

Mr. NATCHER. Dr. Kotin, do you believe asbestos may be causing some cases of lung cancer? Is it true there is a good deal of asbestos in our general environment and in the atmosphere? Isn't it a fact, Dr. Kotin, that the inhalation of even one asbestos fiber can cause a serious respiratory problem, perhaps even lung cancer?

Dr. KOTIN. Occupational exposure to asbestos is associated with an increased risk to lung cancer, and, within the framework of current knowledge, asbestos may be said to cause some cases of lung cancer. There have been several recent studies in which the lungs, obtained either at autopsy or surgery from human subjects not occupationally exposed to asbestos, have shown the presence of fibrous material that has the appearance of asbestos. In addition, bodies having microscopic characteristics of asbestos bodies have also been observed.

Asbestos fibers have been demonstrated in the lungs of urban dwellers in Cape Town, South Africa; Montreal, Canada; Pittsburgh, Pa.; Miami, Fla.; and New York, N.Y. The occurrence of these bodies varied from 20 to 30 percent specimens in some studies to as high as 50 percent in others.

Data at present are inadequate to state with certainty that the inhalation of one asbestos fiber can cause serious respiratory problems or even lung cancer. Quantitative studies are now in progress in some laboratories to determine these matters.

Mr. NATCHER. Have you any plans to have your Division make investigations to determine whether asbestos may be hazardous to man?

Dr. KOTIN. We are certainly concerned with the question as to the extent to which asbestos may be a health hazard. The Division, through its epidemiology program, is participating in the occupational studies now in progress in the Public Health Service. The completion of the phase II construction of the NEHSC will make possible the utilization of total-body exposure chambers. Inhalation studies using experimental animals exposed to fibrous materials including asbestos are planned at present; though, of course, the knowledge gained during the next 2 years may cause us to alter our specific research plans. Individual scientists, including myself, are consulting with scientists at universities now engaged in inhalation studies on asbestos.

Mr. NATCHER. Dr. Kotin, thank you very much.

Mr. HULL. Dr. Kotin, I would like to concur in Mr. Natcher's statement concerning your ability and hope for mutual understanding, if I may.

SMOKING AND HEALTH

The 1967 Public Health Service review entitled "The Health Consequences of Smoking" states on page 35 that the typical characteristics of human squamous-cell lung cancer have not been experimentally pro-

duced by tobacco smoke in animals and goes on to say that this may never be achieved not only because it may not be possible to duplicate man's smoking action in animals, but also because of "differences in cellular response" between man and animals. Do you agree with that observation?

Dr. KOTH. The question is, Is there any reason why cigarette smoke should not be capable of inducing lung cancer in experimental animals; is that the question?

Mr. HULL. Yes.

Dr. KOTIN. I believe under the appropriate conditions that if, indeed, cigarette smoking is the initiating and promoting cause of lung cancer, an experimental model can be developed.

Mr. HULL. Would you also agree that the cellular response of the tissues of the skin of mice is probably different from that of the human lung tissues?

Dr. KOTIN. At the cellular level; yes, sir.

Mr. HULL. In other words, is it correct to say that the fact that condensates of tobacco smoke can produce tumors on the skin of mice is not a scientifically valid demonstration that cigarette smoke can produce lung cancer in man?

Dr. KOTIN. No, I think that is going too far, sir. I think for other agents which we know can produce tumor on the skin of mice, that have unequivocal evidence of producing tumors of the lung in animals, there are examples where this is a fine indicator. That is correct.

Mr. HULL. When the statement is made that cancer-producing chemicals are present in cigarette smoke, it means only that these chemicals will produce cancer in some animals and under experimental conditions; is that correct?

Dr. KOTIN. That is correct.

Mr. HULL. In view of the fact that there are differences in cellular response between animal tissues and human tissues, isn't it a fact that any effects produced in animals with tobacco smoke or some constituent of smoke, may not occur in man?

Dr. KOTIN. I would say it would be likely to occur in man.

### COOPERATION WITH TOBACCO INDUSTRY

Mr. HULL. Now, Dr. Kotin, do you have an opinion with regard to cooperation between HEW and the tobacco industry?

Dr. KOTIN. Yes, a very strong one. I think it is almost indispensable to the solution of the problem.

Mr. HULL. It has occurred to me during these hearings that some of the statements being made by the National Clearinghouse and others go beyond the scientific facts. Don't you think that this makes it more difficult to get cooperation?

Dr. KOTIN. I think for the record, first, as a component of NIH, our activities, except for being under the same Public Health Service umbrella, are unrelated to the activities of the clearinghouse.

From the point of view of the effect of clearinghouse statements on the cooperative index, the efficiency of information transfer between science and industry and science and government, I have not found it to be low or poor. I have welcomed scientists from industry in our Division, and when I visit scientists in industry labs, the welcome is most cordial.

Mr. HULL. Doctor, would you have any suggestions to make as to how HEW could get away from saying on the one hand that something has been established and then asking for substantial funds to do research on the same subject?

Dr. KOTIN. I think this is more or less the history of the evolution of control of disease. The establishment of the existence of a disease does not carry with it the inevitable corollary that you can do nothing about it. In fact, however, when you want to commit the resources to doing something about something—independent of what the problem is—you should have a body of information to warrant this effort.

I would submit at this stage of the game the information—at least to me—would be such that an effort to do something about it is not only warranted, but highly desirable.

OTHER RESEARCH ON SMOKING AND HEALTH

Mr. HULL. How many different kinds of research programs dealing with tobacco and health, Government supported or not, are you familiar with, Doctor?

Dr. KOTIN. I guess most would be it.

Mr. HULL. You can put it in the record. Such as AMA, Agriculture, NCI, your own, Council for Tobacco Research, et cetera.

Dr. KOTIN. I will be glad to answer that for the record.

(The information requested follows:)

As I described in my testimony earlier, I am aware of the research program being supported by the National Institutes of Health. In answer to the broader aspects of the question, through my membership on the American Medical Association Committee for Research on Tobacco and Health, I am quite specifically aware of its activities. This committee is most particularly supporting research in the areas of chronic obstructive respiratory disease and degenerative respiratory changes and the cardiovascular effects of tobacco. Studies are being supported in private research institutions as well as university and medical school laboratories. The Department of Agriculture is concerned with providing biological scientists with tobacco grown under controlled conditions so that the effects of genetic modification of tobacco plants as well as manipulation during growing, curing, and manufacturing can be studied. Further, studies related to the use of pesticides, suckering agents, and microbiological contaminants depend on Department of Agriculture cooperation. The Council for Tobacco Research (U.S.A.) is concerned with a broad program involving the direct effects resulting from tobacco exposure as well as studies of many human factors associated with relatively longer life and with relatively earlier death in human populations. They are trying to find out how habits other than smoking tend to cluster with smoking or with nonsmoking or how these may serve singly or in groups as mathematical predictors of longevity. They also are supporting work to develop new mathematical methods of handing large multifactor studies in the field of epidemiology.

Mr. HULL. What is being done by each of these programs, to the extent you haven't already told us?

Dr. KOTIN. Again, I think I could supply this for the record because each of the individual programs has a segment of the problem peculiar to the people who are responsible for it.

Mr. HULL. Would you say then that these are all pretty sound programs?

Dr. KOTIN. I would say that all programs in tobacco and health are probably no different than programs in other areas of biology. There is brilliant work, pedestrian work, and probably some that doesn't quite measure up.

Mr. HULL. Would you tell us how these programs are coordinated?

Dr. KOTIN. These programs are coordinated by formal exchanges of information including reprint exchange and conferences, by informal joint meetings and contacts, personal associations and access to central repositories of scientific information. The AMA Committee for Research on Tobacco and Health and the Council for Tobacco and Research exchange listings of research projects by title and investigator. Research supported by the PHS as well as by other recognized granting agencies including various foundations and other components of Government are listed in the Scientific Information Exchange. The title of the investigation, the name of the investigator, and brief abstracts of the proposed research are available from S.I.E. In addition, joint membership by scientists on several committees provides important communication. For example, one scientist is a member of the AMA committee, a member of the Scientific Advisory Board of the Council for Tobacco Research (U.S.A.), and in addition serves on one of the advisory groups to the U.S. Public Health Service.

In the past, I have served on the Scientific Advisory Board of the Tobacco Research Council; I am at present on the AMA Committee on Smoking and Health and share responsibility for the NIH program in tobacco and health. In addition, my associates and I are advisers to the Department of Agriculture in relation to research support at the University of Kentucky. The lung cancer task force membership includes representatives from the Department of Agriculture, private research organizations, and the tobacco industry. Thus, coordination of these activities is carried out through formal administrative structures as well as through the exchange of information resulting from publication of research findings in the scientific literature.

Mr. HULL. Don't you believe more could be done by the Government to cooperate with the tobacco industry in the area of smoking and health?

Dr. KOTIN. This is almost a policy matter, and I am perhaps the wrong one to ask because from the days of my tobacco industry research committee membership my relationships with the industry have been so cordial that it has to be brought to my attention that there really isn't this cordiality up and down the line.

Mr. HULL. My final question is, what do you suggest to improve on the present situation?

Dr. KOTIN. In relation to industry?

Mr. HULL. Yes, and you can put that in the record if you like.

Dr. KOTIN. One, I think industry representatives are, from a technological point of view—policywise—indispensable to the development of the scientific program within the Federal Government, and I think Dr. Endicott has emphasized his successful efforts to get industry representatives to deliberate and participate in programs. The Division certainly does this in terms of the body of information the industry has. It is, first, not only deeper than available from other sources, but it can provide an effective base from which we can build so there will be as little duplication as one can achieve.

Mr. HULL. Thank you, Doctor.

JUSTIFICATION MATERIAL

PUBLIC HEALTH SERVICE

Environmental Health Sciences

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $17,289,000 | $18,099,000 |
| Unobligated balance reserve | -264,500 | --- |
| Total | 17,024,500 | 18,099,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| | Grants: | | | | | | |
| 105 | Research | | $8,611,000 | | $8,622,000 | | +$11,000 |
| | General research support grants | | (547,000) | | (551,000) | | (+4,000) |
| | Environmental Health Sciences Institute | | (3,000,000) | | (3,000,000) | | --- |
| 109 | Fellowships | | 100,000 | | 200,000 | | +100,000 |
| 111 | Training | | 3,795,000 | | 3,892,000 | | +97,000 |
| | Direct operations: | | | | | | |
| 113 | Laboratory and clinical research | 128 | 3,749,500 | 182 | 4,538,000 | +54 | +788,500 |
| 118 | Review and approval of grants | 23 | 420,000 | 26 | 449,000 | +3 | +29,000 |
| 119 | Program direction | 20 | 349,000 | 24 | 398,000 | +4 | +49,000 |
| | Total obligations | 171 | 17,024,500 | 232 | 18,099,000 | +61 | +1,074,500 |
| | Unobligated balance, reserve | 5 | 264,500 | --- | --- | -5 | -264,500 |
| | Total, obligations and balance | 176 | 17,289,000 | 232 | 18,099,000 | +56 | +810,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions | 171 | 232 | +61 |
| Full time equivalent of all other positions | 3 | 3 | ... |
| Average number of all employees | 135 | 205 | +70 |
| 11 Personnel compensation: | | | |
| Permanent positions | $1,111,000 | $1,992,000 | +$881,000 |
| Positions other than permanent | 33,000 | 22,000 | -11,000 |
| Other personnel compensation | 7,000 | 6,000 | -1,000 |
| Total personnel compensation | 1,151,000 | 2,020,000 | +869,000 |
| 12 Personnel benefits | 116,000 | 208,000 | +92,000 |
| 21 Travel and transportation of persons | 116,000 | 160,000 | +44,000 |
| 22 Transportation of things | 51,000 | 75,000 | +24,000 |
| 23 Rent, communications, and utilities | 277,000 | 350,000 | +73,000 |
| 24 Printing and reproduction | 13,000 | 20,000 | +7,000 |
| 25 Other services | 462,500 | 173,000 | -289,500 |
| Project contracts | 700,000 | 400,000 | -300,000 |
| Services of other agencies | ..... | ..... | ..... |
| Payment to "National Institutes of Health management fund" | 1,057,000 | 1,351,000 | +294,000 |
| 26 Supplies and materials | 330,000 | 328,000 | -2,000 |
| 31 Equipment | 245,000 | 300,000 | +55,000 |
| 41 Grants, subsidies, and contributions | 12,506,000 | 12,714,000 | +208,000 |
| Total obligations by object | 17,024,500 | 18,099,000 | +1,074,500 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $17,289,000 |
| Unobligated balance, reserve | -264,500 |
| 1968 total estimated obligations | 17,024,500 |
| 1969 estimated obligations | 18,099,000 |
| Total change | +1,074,500 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of 1968 pay raise cost | --- | --- | --- | $37,000 |
| 2. Annualization of new positions authorized in 1968 | --- | --- | --- | 587,000 |
| 3. One additional day's pay in 1969 | --- | --- | --- | 9,000 |
| B. Program | | | | |
| 1. Research grants | --- | $8,611,000 | --- | 11,000 |
| 2. Fellowships | --- | 100,000 | --- | 100,000 |
| 3. Training grants | ---- | 3,795,000 | --- | 97,000 |
| 4. Laboratory and clinical research | 128 | 2,869,500 | 54 | 489,000 |
| 5. Review and approval of grants | 23 | 311,000 | 3 | 19,000 |
| 6. Program direction | 20 | 281,000 | 4 | 23,000 |
| Total program increases | --- | --- | 61 | 739,000 |
| C. Payment to the "National Institutes of Health management fund" for centrally furnished services: | | | | |
| 1. Laboratory and clinical research | --- | 880,000 | --- | 267,000 |
| 2. Review and approval | --- | 109,000 | --- | 5,000 |

| Increases | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| 3. Program direction..... | --- | $68,000 | --- | $22,000 |
| Subtotal, management fund increases..... | --- | --- | --- | 294,000 |
| Total increases.... | --- | --- | 61 | 1,666,000 |
| **Decreases** | | | | |
| A. Built-in | | | | |
| 1. Non-recurring other services..... | --- | --- | --- | -289,500 |
| 2. Non-recurring supplies and materials..... | --- | --- | --- | -2,000 |
| B. Program | | | | |
| 1. Reduction in project contracts. | --- | --- | --- | -300,000 |
| Total decreases..... | --- | --- | --- | -591,500 |
| Total net changes requested. | --- | --- | --- | 1,074,500 |

Explanation of Changes

Research grants--The increase of $11,000 will provide $4,000 for general research support grants and $7,000 for the increased cost of regular research projects in 1969.

Fellowships--The increase of $100,000 will provide for the award of 5 additional fellowships in 1969 and increased costs for special awards.

Training grants--The increase of $97,000 will provide for the initiation of 1 additional program and increased costs for some ongoing programs.

Laboratory and clinical research--The program increase of $489,000 and 54 positions will provide staffing for the establishment of an electron microscopy research program and a modest instrumentation development program, as well as expansion of the existing laboratories.

Review and approval of grants--The increase of $19,000 provides 3 new positions to strengthen the scientific review of grant programs.

Program direction--The increase of $23,000 and 4 new positions will provide additional supporting staff for the Director of the Division and his staff.

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act | |
| Section 301--Research and Investigation, In General..... | Indefinite |
| Title III, Part A--Division of Environmental Health Sciences... ..... | Indefinite |

PUBLIC HEALTH SERVICE ACT

Title III, General Powers and Duties of Public Health Service, Part A, Research and Investigation.--

"Sec. 301. The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams."

Justification

ENVIRONMENTAL HEALTH SCIENCES

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 171 | $1,267,000 | 232 | $2,228,000 | +61 | +$961,000 |
| Other expenses | | 15,757,500 | | 15,871,000 | | +113,500 |
| Total | 171 | 17,024,500 | 232 | 18,099,000 | +61 | +1,074,500 |

General Statement

Introduction

In the interval since the end of World War II there has developed a growing national awareness of the enormous impact which man is having on his physical and social environment. As has been pointed out in numerous national studies and in the scientific literature, man is now capable of adversely affecting his environment in a manner that increases its hazard to health.

The growth in American population projected over the next twenty years and the increasing complexity of American society makes imperative immediate effort directed to the procurement of answers to fundamental questions of environment and health which will not only affect our lives but those of our children in the years to come.

The Division of Environmental Health Sciences, with its intramural program the National Environmental Health Sciences Center, was established in response to both the threat and the challenge of the future. Its research programs have as their goal the advancement of fundamental knowledge and the development of a scientific base which will serve to provide answers to questions which man's interaction with his environment will inevitably generate in the coming decades.

Extramural Research and Training

The extramural activities of the Division of Environmental Health Sciences have a three-fold aim. First, support is provided for numerous independent explorations of the various facets of environmental health problems. Included are fundamental and applied research, utilizing a broad spectrum of scientific disciplines, such as chemistry, pathology, toxicology, general biology, biometry, epidemiology, clinical sciences, engineering and the physical sciences. Second, opportunities are made available for specialized training in order to enlarge the Nation's supply of highly-trained research scientists in the field of environmental health. Third, grants, make it possible to take advantage of university capabilities to mobilize multidisciplinary concentrations of scientific talent for research and training that requires new methodology, new

instrumentation, and innovative approaches to complex problems.

The research and training sponsored extramurally by the Division are directed toward quantification of hazards, elucidation of mechanisms of biological effects, and ultimate indication of possible methods for protection against hazards either through (a) establishing a need and basis for requiring removal of an agent from the environment, (b) identifying and verifying non-toxic concentrations of the agent in the environment, or (c) developing host-buffering techniques or other biologically feasible procedures for protection of the host.

Grant-supported research and training are an essential means through which the Division helps to achieve a national focus on the mission of assessing actual and potential risks. These risks may be associated with exposure to environmental agents of all forms (chemical, physical, and biological) entering the host through all portals (skin, respiratory tract, and gastrointestinal system).

Intramural Research

The National Environmental Health Sciences Center, the intramural program of the Division of Environmental Health Sciences, was created for the purpose of investigating at the fundamental level the long-term and subtle effects of environmental agents potentially hazardous to man. These studies will be directed to the development of a base for establishing standards and devising remedial measures. The increasing complexity of our environment makes it imperative to view the problems of environmental hazards from the vantage point of total health effects. It is this information that is necessary before an effective foundation can be constructed so as to assure protection of exposed populations. Complementing the experimental laboratory studies, the Center will engage in long-term epidemiological studies of populations with unusual environmental experiences or unique morbidity and mortality experiences. The third aspect of the Center's projected program will include a clinical research program which will have as its primary objective the study of individuals and samples from defined population groups for the purpose of determining the effects of exposure to low concentrations of known or suspect environmental toxic agents over long periods of time. These studies will seek to identify the basis for variations in response to environmental insults and assess on an ongoing basis the compatibility of experimental laboratory data with human data. It is hoped that this approach will assure maximum extrapolation of laboratory findings, as well as provide important principles and generalizations, to permit the development of effective guidelines with which to judge the myriad new agents constantly entering our environment.

In summary, the Center will provide a central facility for research on the total health effects of physical, chemical and other environmental factors to which the American people are exposed.

The function of the Center is to identify harmful agents in the environment, discover the mechanisms by which they affect an individual's health, and develop data on the effects of chronic exposure, thereby providing a scientific base upon which control measures can be developed. The seven classes of

environmental agents on which research is now being initiated are natural products, metal compounds, hydrocarbon reaction products, tobacco smoke constituents, polymer dusts, pesticides, and pesticide synergists.

The narrative material which follows gives greater detail regarding both current and planned investigations for support and conduct either through grants or contracts, or in the Division's own laboratories. The programs of the Division are discussed here in terms of the mechanism employed for their support. However, these programs are viewed and planned in terms of a total national program with each component being complimentary to the others, and all aimed at the understanding of the hazards to health resulting from man's interaction with his biological environment.

The DEHS is requesting a total of $18,099,000 for 1969, an increase of $1,074,500 over 1968. This increase will strengthen the fellowship and training grant programs and maintain research grants at the same level of effort. Funding for an additional 61 positions is provided allowing the expansion of the National Environmental Health Sciences Center into the additional space to be available in 1969 at the Research Triangle Park, North Carolina. This expansion will allow the initiation of further elements of the planned intramural research program of the Division.

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Research projects | $5,064,000 | $5,071,000 | +$7,000 |
| Special programs | 3,547,000 | 3,551,000 | +4,000 |
| Total research grants | 8,611,000 | 8,622,000 | +11,000 |

Introduction

These funds support research activities in the environmental health sciences within universities, hospitals, research institutions, and other public or private nonprofit institutions. Grants are awarded to support investigations aimed at defining and understanding effects upon human health of noxious agents in the environment. This involves research that ranges from smaller and circumscribed projects to broad and composite programs that coordinate the capabilities of scientists with diverse training and experience.

Program Plans in 1968 and 1969

Projects supported by the Division through regular research grants in both 1968 and 1969 will be oriented largely to (1) defining the physical, biological, and chemical hazards of the environment with particular relevance to the well-being of man; (2) determining the significance of these agents to the etiology of disease in man with special emphasis on exposure to low levels of environmental hazards; and (3) developing new or improved instrumentation and methodology for analysis and characterization of the biological effects of known and potentially hazardous substances.

The following problem areas indicate in specific terms the types of research activity that will continue to be emphasized:

There is a critical need for tests that can be applied harmlessly and conveniently in the intact animal or human being to characterize effects of environmental agents on physiological status and to make interspecies comparisons of response to a given material. Currently available techniques are frequently inadequate for detecting low-level and subtle effects resulting from chronic exposure to substances that may be present in the environment in low concentrations.

The problem of mutagenesis in the human population represents an important problem in public health. Man is constantly exposed to substances such as food additives, drugs, herbicides, and insecticides that have received only limited testing for mutagenic properties. This situation merits concern because many known mutagens are not particularly toxic at doses where mutational damage to the DNA occurs. The importance of dose in the induction of mutations as well as in the interpretation of mutagenic effect in experimental species in relation to man is critical in the interpretation of experimental data.

Research on the extent of interaction of pesticides and drugs that are ordinarily taken over extended periods of time has been strongly recommended by the President's Science Advisory Committee in a report entitled "Use of Pesticides." The Division is continuing to support promising studies that will indicate the capability of various combinations of pesticides with other agents to produce interaction at usually encountered dose levels.

The metabolism of insecticides is known to be a major determinant of their relative toxicities. The increasing extent of exposure of man and animals to insecticides accordingly underscores the urgency for a fuller understanding of the metabolic and toxicologic interrelations among such compounds. To facilitate such research, the Division is supporting work on the elaboration of extremely sensitive analytic tools for identification and classification of minute quantities of pesticides extracted from tissues, soils, animal and plant products, as well as the effects and interactions of pesticides in mammalian systems.

Pulmonary disease has become an increasingly significant source of morbidity and mortality in the population of the United States. Research by a grantee of the Division of the physiological fate of aerosols in the pulmonary system has led to two new procedures that promise to be useful diagnostic aids in such respiratory diseases as bronchitis and emphysema. These procedures have a potential for defining the extent and rate of progression of such diseases. These measurements can aid in elucidating the relationship of these diseases to exposure to environmental factors such as air pollutants. In this instance a long-standing interest in aerosols, which was originally oriented toward their role as carriers of toxic materials, has permitted their exploitation for diagnostic purposes.

Funds for regular projects are largely committed to the continuing support of ongoing studies. Since competing funds available in 1968 and 1969 will be exceeded by the anticipated costs of renewing projects that terminate in those years, expansion of ongoing research will be approved only under exceptional circumstances. In addition, an extremely limited number of high priority new studies will be activated through reduction or termination of projects now under way.

Special programs. University-based Environmental Health Sciences Institutes have been established in response to the multivariable nature and complexity of environmental health problems. These problems require for their solution a broad spectrum of research endeavor which includes the following: target research and undifferentiated research; field studies and studies performed in laboratory and clinical facilities; routine work and highly creative work, investigations by individuals and by teams; and, availability of skills representing the biological, physical, and social sciences, as well as the various disciplines of clinical medicine. Few institutions have programs that cover more than a small fraction of this spectrum.

With their activities concentrated on environmental health problems, centers not only can provide types of specialized training relatively unavailable elsewhere, but can also help to meet the national need for attractive and stable career opportunities for research in the environmental health sciences. In addition, centers are uniquely able to promote the close integration of environmental technology with an underlying science base.

In 1968, the Division is supporting five EHS Institutes that have operational status. Reflecting the research interests of their key personnel, the programs of these centers are focused on such problem areas as toxicology, the biology of natural systems, environmental systems analysis, environmental pollution and ecology, occupational health, and environmental carcinogenesis. Four other institutions are involved in pilot efforts to determine the feasibility and developmental opportunities for undertaking a long-term commitment to operating an institute for environmental health research and training. The estimate for 1969 remains at the same level as for 1968. This level of funds would permit continuation of the five ongoing Institutes and a transition to operational status for those currently-active developmental programs that will require renewal support.

Included in the unique features of the EHS Institutes are their specialized skills, their specially tailored facilities, and an effective array of disciplines that can be applied to a defined segment of the total environmental health problem. The research at each EHS Institute complements the programs at the other EHS Institutes and at the National Environmental Health Sciences Center in North Carolina. Each is designed to be a part of the whole, within the availability of our resources.

The increase of $4,000 in 1969 for General Research Support represents the Division's proportionate share of the increase in this program.

## Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Noncompeting continuations | 62 | $4,016,000 | 61 | $4,023,000 | -1 | +$7,000 |
| 2. Competing projects | 11 | 999,000 | 12 | 988,000 | +1 | -11,000 |
| 3. Supplementals | (1) | 49,000 | (2) | 60,000 | (+1) | +11,000 |
| 4. Subtotal | 73 | 5,064,000 | 73 | 5,071,000 | 0 | +7,000 |
| 5. General research support | | 547,000 | | 551,000 | | +4,000 |
| 6. Environmental Health Sciences Institutes | | 3,000,000 | | 3,000,000 | | 0 |
| 7. Total research grants | | 8,611,000 | | 8,622,000 | | +11,000 |

## Research Grants Program Analysis

| Fields | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Toxicology | $2,167,000 | $2,187,000 | +$20,000 |
| Pesticides | 2,098,000 | 1,888,000 | -210,000 |
| Natural products | 325,000 | 390,000 | +65,000 |
| Synthetic organics | 218,000 | 283,000 | +65,000 |
| Heavy metals | 174,000 | 231,000 | +57,000 |
| Smoking and health | 82,000 | 92,000 | +10,000 |
| Subtotal regular program | 5,064,000 | 5,071,000 | +7,000 |
| General research support grants | 547,000 | 551,000 | +4,000 |
| Environmental Health Sciences Institutes | 3,000,000 | 3,000,000 | 0 |
| Total research grants | 8,611,000 | 8,622,000 | +11,000 |

## Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total Fellowships..... | $100,000 | $200,000 | +$100,000 |

### Introduction

The Division was authorized during 1967 to award a limited number of research fellowships with funds that were reprogrammed from the training grants activity.

Fellowships complement training grants by providing opportunities in departments which do not have training grant support. A wider selection of training disciplines, faculty sponsors, and locations is thereby afforded.

The purpose of the fellowship program is to augment the numbers of scientific investigators and teachers trained in the basic disciplines and sciences for use in attacking problems in the field of environmental health research. The program is competitive at the national level and provides opportunities for full-time study and research training for the best qualified predoctoral, postdoctoral, and advance investigator applicants.

### Program Plans for 1968 and 1969

Fellowships presently supported include predoctoral, postdoctoral and special awards. The emphasis will shift somewhat in 1969 from predoctoral to postdoctoral awards although additional predoctoral awards are anticipated and the cost of special awards will increase. In addition to stipends, funds are provided for dependents, tuition and fees, and necessary travel. Host institutions receive a supply allowance to defray the expenses for research supplies and equipment available to the fellow.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting..... | 0 | 0 | 11 | $103,000 | +11 | +$103,000 |
| b. Competing..... | 0 | 0 | 1 | 6,000 | +1 | +6,000 |
| 2. Supplementals..... | (2) | $1,000 | (2) | 1,000 | 0 | 0 |
| 3. New awards..... | 16 | 99,000 | 9 | 90,000 | -7 | -9,000 |
| 4. Total fellowships..... | 16 | 100,000 | 21 | 200,000 | +5 | +100,000 |

(Fellowships (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Predoctoral..... | 7 | $38,000 | 9 | $75,000 | +2 | +$37,000 |
| 2. Postdoctoral..... | 5 | 33,000 | 8 | 81,000 | +3 | +48,000 |
| 3. Special..... | 4 | 29,000 | 4 | 44,000 | 0 | +15,000 |
| 4. Total fellowships..... | 16 | 100,000 | 21 | 200,000 | +5 | +100,000 |

## Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Training grants..... | $3,795,000 | $3,892,000 | +$97,000 |

### Introduction

The graduate research training grants program of the Division of Environmental Health Sciences is broad and diverse. It has a three-fold goal: (1) to increase the numbers of highly qualified scientists primarily concerned with environmental health; (2) to enable institutions to strengthen and to enrich their research training capabilities; and (3) to expand opportunities for environmental health research training in a greater number of graduate institutions throughout the United States. These grants permit local identification and selection of candidates with research potential, as well as provide funds for payment of stipends.

### Program Plans for 1968 and 1969

The programs to be supported in 1968 fall into the following fields: biochemical toxicology, pesticide biology, environmental engineering, microbiology, occupational health, and ecology. It is expected that new grants awarded in 1969 will show a relative decrease in those aspects of ecology, environmental engineering, and pesticide biology not immediately relevant to the health of man.

In 1968, the Division expects to provide training for approximately 450 full-time trainees. The increase of $97,000 in 1969 will provide for increasing costs of existing grants plus 1 additional grant and should provide for approximately 12 additional full-time trainees.

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting.... | 36 | $2,933,000 | 49 | $3,297,000 | +13 | +$364,000 |
| b. Competing..... | 6 | 260,000 | 4 | 250,000 | -2 | -10,000 |
| 2. Supplementals..... | (2) | 65,000 | (2) | 50,000 | 0 | -15,000 |
| 3. New programs..... | 14 | 517,000 | 4 | 275,000 | -10 | -242,000 |
| 4. Scientific evaluation.. | (1) | 20,000 | (1) | 20,000 | 0 | 0 |
| 5. Total training grants.. | 56 | 3,795,000 | 57 | 3,892,000 | +1 | +97,000 |

Training Grants (by program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Graduate..... | 56 | $3,775,000 | 57 | $3,872,000 | +1 | +$97,000 |
| 2. Scientific evaluation.. | (1) | 20,000 | (1) | 20,000 | 0 | 0 |
| 3. Total training grants.. | 56 | 3,795,000 | 57 | 3,892,000 | +1 | +97,000 |

Laboratory and Clinical Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 128 | $825,000 | 182 | $1,702,000 | +54 | +$877,000 |
| Other expenses | | 2,924,500 | | 2,836,000 | | -88,500 |
| Total | 128 | 3,749,500 | 182 | 4,538,000 | +54 | +788,500 |

Introduction

The National Environmental Health Sciences Center, the intramural research program of the Division of Environmental Health Sciences, is located in Research Triangle Park, North Carolina. Here are located all of the Center's research units except for the Occupational Studies Group. In addition, the establishment of an epidemiologic and biometric research operation is planned. The Center is essentially self-supporting in terms of having available to it engineering, research, and administrative support staff to provide assistance to the intramural research operations.

The National Environmental Health Sciences Center will serve as the focal point of a projected nationwide collaborative effort for research in environmental health problems.

The scope of research of the Center is broad and is structured to study at the fundamental level the long-term and subtle effects of environmental agents potentially hazardous to man.

Three major goals of the Center's program are:

1. The development of experimental methodologies, both laboratory and demographic, to meet existing needs which are not being met by traditional approaches.

2. Characterization of needs and solution of problems of environmental health with the totality of the problem providing the guidelines for protocol design and research pursuit. This permits the simultaneous application of diverse discipline and categorical approaches and a constant monitoring of the state of progress at any point in time. For each such investigation, this assures that significant areas are not being neglected either by default, or intent.

3. Maintenance of flexibility of programming so that continuous parallel assessment of laboratory and epidemiological research can be accomplished with minimal loss in time. The significance of each in relation to the other is under constant review to assure maximum effectiveness of both.

The interdependence of disciplines and the assured scientific exchange inherent in the problem-solving approach has been a recognized need in the

biological sciences. The unprecedented accomplishment in the physical sciences has been acheived in large measure through the marriage of disciplines in problem-solving teams. Industry has long and successful experience in the use of this technique. The National Environmental Health Sciences Center, in contrast to traditional academic structure, is geared to this approach through the accumulation and utilization of data derived from many sources - in-house studies, university centers, and the scientific community in general, all of which provide information of a complementary character.

It is the function of the Center to identify harmful agents in the environment, discover the mechanisms by which they affect an individual's health, and develop understanding of the effects of chronic exposure, thereby providing a scientific base upon which standards can be developed and control measures can be established. The seven classes of environmental agents for which we are now initiating research programs are natural products, metal compounds, hydrocarbon reaction products, tobacco smoke constituents, polymer dusts, pesticides, and pesticide synergists. Within each of these areas a number of agents will be selected for study based on laboratory observations of adverse effects in animals exposed to a given agent and based on epidemiological studies suggesting adverse effects on population groups exposed to these agents in the environment.

Program Plans in 1968

The staff of the cell biology branch is currently involved in studies of natural products and with enzyme induction and metabolism of toxicants.

The work in natural products is concerned primarily with toxins produced by fungi on foodstuffs. Preliminary studies have been initiated on the production of toxins by certain fungi in fruit and vegetable crops before and after harvest. Cultures of all fungi prevalent in food crops are being acquired from farm commodities by direct isolation. The cultures are fed to mice, which are kept under surveillance for symptoms of toxicity. Toxin-producing fungi will be cultured in quantities sufficient for isolation and identification of the toxins.

Cultures of mammalian cells have been established for the study of enzyme induction by certain chemicals. Preliminary experiments are underway to characterize nucleoproteins believed to play a role in the inductive process. The objective of these studies is to elucidate the mechanism by which enzymes responsible for detoxication of drugs and chemicals are induced. Because this is a primary defense mechanism against environmental pollutants, understanding of the induction process per se and of the factors which contribute to its operation becomes increasingly important as the body load of harmful foreign compounds from environmental sources increases.

Pilot studies with selected chemicals are being initiated to establish a model system for studying the effects of toxicants on the structure, function and biogenesis of mitochondria, which play a key role as regulators of the metabolism of cells. Thus, chemical agents that interfere with mitochondrial activity may also affect cellular growth and function.

The analytical and synthetic chemistry branch augments the functional

programs of the Center by developing new and improved analytical techniques for determining micro qualitative and quantitative determination of many chemicals. It aids in determining purity and stability of chemicals, identifies trace metals and other environmental substances, such as flavors, food additives, or pesticides. Studies are also being carried out on the degradation products of some of these chemicals. The environmental parameters of pesticides are being elaborated with regard to both rates of degradation and the identity of the decomposition products. Natural products with toxic properties are being isolated and characterized. Pesticide synergists are being tracked by means of tracer techniques from intake to their excretion by experimental animals.

The animal science and technology branch provides, maintains, and monitors all animals used in the Center research programs. The branch is also currently engaged in several research programs both on its own and in conjunction with the chemistry and cell biology branches. Several pesticides and other environmental chemicals are being studied in an effort to determine their effect on immune response mechanisms. Efforts are being made to determine whether rival infections are enhanced or reduced by exposure to these environmental chemicals. Mechanisms of interactions will be explored using tissue culture techniques and by examining the altered physiologic and pathologic responses of laboratory animals.

The objectives of the pharmacology and toxicology branch are five-fold. First, the branch will identify the effects of environmental agents on living systems. Second, it will assess the significance of initial interactions in terms of potential or actual end results. Third, it will attempt to understand the mechanisms by which the initial interactions produce the end results. Fourth, it will seek practical means of control over the sequence of events so that it might be possible to cancel, ameliorate, or otherwise modify the final outcome, in a potentially beneficial manner. Fifth, it will attempt to gain an understanding that will permit the prediction of those agents or classes of agents and their possible effects that may be harmful.

The program is concerned with the chronic, the less obvious, and unexpected effects, as well as the acute and the more obvious. By their nature, acute effects are relatively easy to detect and to associate with a causative agent. Chronic effects are not only more difficult to associate with a specific causative agent, but they are also readily modified by secondary interactions. Time, in the chronic effect, introduces the potentiality of greater variation in the type of manifest response.

Either the initial or the manifest response could be detrimental or beneficial, permanent or transient, cumulative or non-cumulative, immediate or delayed. The response could also vary in intensity or in type, depending upon the genetic composition of the organism. Finally, the organism might become sensitized or tolerant to the environmental agent. Each of these alternatives will be considered.

The pharmacology and toxicology branch, presently staffed only in the area of growth and development, has work underway on the testing of selected compounds for their ability to interfere with normal pre-natal and post-natal development, the ability of chemicals and other environmental agents to produce congenital

malformations, and the transfer of compounds through the placenta and excretion of compounds in maternal milk.

In contrast with many studies of the occupational environment, the emphasis in the program of the Occupational Studies Group is placed on the identification of disease states in man which appear many years after exposure to causative agents. While evidence accumulative to date indicates that many industrial processes may be implicated as the cause of disease, not enough research has been done in this area due to lack of data resources, unavailability of scientific and administrative support, and limited cooperation of industry in undertaking such studies. The growth in number and reliability of data sources for identification and follow-up of exposed populations, as well as a spirit of willingness and cooperation on the part of industry, have now made it feasible to initiate an occupational studies program. The current research program is studying uranium miners and millers, steelworkers, coke-oven workers, hard rock miners, chromate painters, smelter workers, and workers exposed to cutting oils.

The Office of Scientific Information maintains intimate contact with program planning and current operations in the operational environmental health regulatory and control programs of the Service. In addition, this office is developing a system of scientific intelligence designed to identify and strengthen sources of information on the existence of environmental hazards, warranting intensive study or research. This office also provides scientific reference services for the intramural scientists.

Program Plans in 1969

At the beginning of 1969, the Center will have gained a total of 16,000 additional square feet of space. By making possible the relocation of existing offices and warehouse space, this additional space will permit the Center to expand in ongoing research programs as well as initiate a select number of new research activities. By the beginning of calendar year 1969, the Center will have available to it an additional 11,500 square feet of space that will permit the initiation of an electron microscopy research program, a modest instrumentation program, and a significant expansion of pathology facilities. This additional space will permit the strengthening and expansion in cell biology and pharmacology and toxicology programs.

In the cell biology program, it is planned to extend studies on the biochemical mechanisms of toxicant action. In addition, the studies on toxicant-induced diseases will be extended to include studies with the chlorinated hydrocarbon insecticides.

In the pharmacology and toxicology branch, a number of additional areas of investigation are planned. Among these are the metabolism of environmental agents in the pregnant animal as well as in the fetus and placenta; biochemical and morphological correlates of low birth weight, increased post-natal mortality, or decreased post-natal growth; and the potential of environmental agents to modify genetically deficient development in a beneficial manner.

In 1969, the Center plans to further explore the development of broadly based programs in both descriptive and analytical epidemiology. In addition

to expanding and strengthening the currently ongoing occupational studies, this expansion will complement planned and ongoing laboratory studies, and provide a guide for future laboratory efforts. Descriptive epidemiology will be primarily concerned with the collection of data on variation in risk to environmentally determined or primarily initiated morbidity; i.e., measure disease and measure the factors. The demographic variables to be studied will include occupation, residence site, age, sex, race, antecedent and concurrent disease, genetic characteristics, etc. Analytical epidemiology will be concerned with the development of individually tailored protocols designed for the purpose of testing hypothesis by statistical correlations on the nature of associations between environmental agents, host characteristics, and the patterns of environmental disease. Together these should permit the testing of ideas concerning the relationship of environmental factors to disease in man particularly in the ranges of low-level exposure where long-term, cumulative effects are evaluated rather than the more obvious acute responses.

This information should provide a base for studies in which the effect of changing a group's experience on disease frequency can be determined. This will permit measuring the effect of the institution of broad public health measures.

The program increase of $489,000 and 54 positions would permit the establishment of an electron microscopy research program and an instrumentation development program, as well as modest expansion of most of the ongoing intramural research programs. An increase of $547,000 is requested for mandatory items such as annualization of new positions authorized in 1968, annualization of the 1968 pay increases and one additional day of pay in 1969. There is also an increase of $267,000 for centrally furnished services from the NIH Management Fund.

The above increases are partially offset by a decrease of $300,000 in project contracts and $214,500 in non-recurring other services and supplies and materials.

## Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 23 | $247,000 | 26 | $271,000 | +3 | +$24,000 |
| Other expenses | | 173,000 | | 178,000 | | +5,000 |
| Total | 23 | 420,000 | 26 | 449,000 | +3 | +29,000 |

### Introduction

This activity, under the Associate Director for Extramural Activities, supports the scientific, administrative, and clerical staffs responsible for the over-all coordination and administration of the Division's grants program.

Functions for which the staffs are responsible include review and evaluation of fellowships, research and training grant applications for presentation to the Advisory Council; liaison with applicants, grantees, advisory bodies, other components of NIH and PHS, and other interested organizations; maintenance of a continuing review of ongoing research and training programs; and the compilation and reporting of scientific and fiscal information relevant to all transactions.

The net increase of $29,000 and 3 positions requested for this activity includes a program increase of $19,000 to provide staff for more thorough scientific review of existing grants and new grant applications, a mandatory increase of $50,000 for annualization of new positions authorized 1968, annualization of 1968 pay increases and one additional day of pay in 1969, and an amount of $5,000 for the increased cost of centrally furnished services from the NIH management fund, partially offset by a decrease of $45,000 in non-recurring other services.

## Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 20 | $195,000 | 24 | $255,000 | +4 | +$60,000 |
| Other expenses | | 154,000 | | 143,000 | | -11,000 |
| Total | 20 | 349,000 | 24 | 398,000 | | +49,000 |

### Introduction

This activity supports the Office of the Director, including the administrative, secretarial, and clerical staffs required for the administration, technical direction and coordination of all division activities; the review of current and proposed programs; the introduction of new knowledge into currently operating programs; and the provision and supervision of centralized administrative services.

Administrative personnel are also concerned with the areas of finance, supply, travel, space utilization, personnel, and management analysis.

The increase of $49,000 and 4 positions requested for this activity includes a program increase of $23,000 to strengthen the management planning and public information functions of the division, a mandatory increase of $36,000 for annualization of 1968 pay increases and one additional day of pay in 1969, and an amount of $22,000 for the increased cost of centrally furnished services from the NIH management fund, partially offset by a decrease of $32,000 in non-recurring other services.

THURSDAY, MARCH 21, 1968.

# GENERAL RESEARCH AND SERVICES

## WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. THOMAS J. KENNEDY, JR., DIRECTOR, DIVISION OF RESEARCH FACILITIES AND RESOURCES
DR. HEINZ SPECHT, DIRECTOR, OFFICE OF INTERNATIONAL RESEARCH
DR. ARNOLD W. PRATT, DIRECTOR, DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimated | 1969 estimated |
|---|---|---|---|
| Personnel compensation: | | | |
| Permanent positions | 2,716 | 3,353 | 3,629 |
| Positions other than permanent | 91 | 207 | 214 |
| Other personnel compensation | 6 | 9 | 10 |
| Total personnel compensation | 2,813 | 3,569 | 3,853 |
| Personnel benefits | 312 | 370 | 383 |
| Travel and transportation of persons | 394 | 456 | 491 |
| Transportation of things | 86 | 83 | 97 |
| Rent, communication and utilities | 172 | 189 | 201 |
| Printing and reproduction | 12 | 125 | 157 |
| Other services | 1,481 | 1,319 | 1,523 |
| Project contracts | 2,127 | 5,576 | 6,576 |
| Payments to "National Institutes of Health management fund" | 847 | 756 | 803 |
| Supplies and materials | 65 | 75 | 153 |
| Equipment | 165 | 161 | 450 |
| Grants, subsidies, and contributions | 59,149 | 66,656 | 72,813 |
| Total obligations | 67,623 | 79,335 | 87,500 |

PERSONNEL SUMMARY

| | | | |
|---|---|---|---|
| Total number of permanent positions | 302 | 338 | 371 |
| Full-time equivalent of other positions | 12 | 19 | 21 |
| Average number of all employees | 273 | 324 | 360 |
| Average GS grade | 7.5 | 7.7 | 7.7 |
| Average GS salary | $8,362 | $8,965 | $8,999 |
| Average salary of ungraded positions | $6,798 | $7,166 | $7,154 |

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimated | 1969 estimated |
|---|---|---|---|
| Program by activities: | | | |
| 1. Division of Research Facilities and Resources: | | | |
| (a) Grants: | | | |
| (1) Research | 51,663 | 57,198 | 62,432 |
| (2) Fellowships | 41 | 200 | 204 |
| (3) Training | 245 | 318 | 326 |
| (b) Direct operations: | | | |
| (1) Collaborative research and development | 701 | 1,974 | 1,978 |
| (2) Review and approval of grants | 1,176 | 1,506 | 1,608 |
| (3) Program direction | 677 | 810 | 867 |
| 2. Office of International Research: | | | |
| (a) Grants: | | | |
| (1) Research | 6,000 | 7,560 | 8,440 |
| (2) Fellowships | 1,200 | 1,380 | 1,411 |
| (b) Direct operations: | | | |
| (1) International research | 1,687 | 3,303 | 3,316 |
| (2) Training activities | 145 | 187 | 187 |
| 3. Division of Computer Research and Technology: Direct operations | 2,477 | 4,555 | 4,784 |
| 4. Engineering development: Direct operations: Program direction | 348 | 344 | 1,347 |
| 5. International Center: Direct operations | | | 600 |
| Total program costs, funded [1] | 66,360 | 79,335 | 87,500 |
| Change in selected resources [2] | 1,263 | | |
| Total obligations | 67,623 | 79,335 | 87,500 |
| Financing: | | | |
| Comparative transfers from other accounts | −3,155 | | |
| Unobligated balance lapsing | 4,054 | 1,806 | |
| New obligational authority | 68,522 | 81,141 | 87,500 |
| New obligational authority: | | | |
| Appropriation | 68,534 | 81,141 | 87,500 |
| Transferred to other accounts | −12 | | |
| Appropriation (adjusted) | 68,522 | 81,141 | 87,500 |
| Relation of obligations to expenditures: | | | |
| Total obligations | 67,623 | 79,335 | 87,500 |
| Receipts and other offsets (items 11–17) | −3,155 | | |
| Obligations affecting expenditures | 64,468 | 79,335 | 87,500 |
| Obligated balance, start of year | 46,414 | 55,354 | 64,329 |
| Obligated balance, end of year | −55,354 | −64,329 | −80,429 |
| Adjustments in expired accounts | −1,608 | | |
| Expenditures | 53,920 | 70,360 | 71,400 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 29,726 | 38,768 | 38,000 |
| Out of prior authorizations | 24,194 | 31,592 | 33,400 |

[1] Includes capital outlay as follows: 1967, $674 thousand; 1968, $161 thousand; 1969, $171 thousand.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $2,431 thousand; 1967, $3,694 thousand; 1969, $3,694 thousand.

Mr. FLOOD. We now have general research and services.

We are pleased to have Dr. James A. Shannon, the distinguished director of the National Institutes of Health, with us, who will attempt to justify this appropriation.

Dr. SHANNON. I have with me Dr. Thomas J. Kennedy, Jr., Director, Division of Research Facilities and Resources.

Mr. FLOOD. What is your position, Doctor?

Dr. KENNEDY. Director of the Division of Research Facilities and Resources.

Mr. FLOOD. You came here in 1965.

Dr. KENNEDY. I took on this job in 1965. I came to the NIH in the fall of 1949.

Dr. SHANNON. Dr. Heinz Specht is Director of the Office of International Research.

Mr. FLOOD. How long have you been on board, Doctor?

Dr. SPECHT. I have been with the Office since 1962. I have been Director of the Office since 1965.

Mr. FLOOD. We are glad to see you.

Dr. SHANNON. Dr. Arnold W. Pratt is the Director, Division of Computer Research and Technology.

Mr. FLOOD. How long have you been at NIH?

Dr. PRATT. I came to the NIH in 1948. I assumed this position in August 1966.

Mr. FLOOD. How did you get this job?

Dr. PRATT. Dr. Shannon honored me with this job, sir.

Mr. FLOOD. Why?

Dr. SHANNON. I thought he was the best man in the country for it.

Then I have Dr. Richard Seggel to my left, who is Executive Officer, National Institutes of Health.

Mr. FLOOD. You are the fellow who really does the work.

Dr. SEGGEL. I help.

Dr. SHANNON. When we come down to the detailed questions, these professional witnesses will be helpful to me.

## GENERAL STATEMENT

Mr. Chairman and members of the committee, this appropriation provides support for five noncategorical areas of activity. These are: the activities of the Division of Research Facilities and Resources; the Office of International Research; the Division of Computer Research and Technology; Engineering Development; and the John E. Fogarty International Center for Advanced Studies in the Health Sciences. I should like to speak to each of the five elements of the "General research and services" appropriation separately, and to summarize the total request at the end.

## DIVISION OF RESEARCH FACILITIES AND RESOURCES

Mr. Chairman, I propose to address myself first to the programs of the Division of Research Facilities and Resources. The mission of this Division is, as you know, not to finance research as such but rather to provide the Nation's scientific community with a basic complement of facilities and resources indispensable for sustaining and advancing the country's research and research training activities. These resource programs underpin a very broad spectrum of science by delivering services needed by scientists across the total panorama of biomedical research.

### GENERAL CLINICAL RESEARCH CENTERS

The General Clinical Research Center program, inaugurated in 1960, provides the facilities and resources in which clinical investigators can study human diseases: to increase the understanding of the nature and natural history of disease, to extend the capability of medical science to treat and manage disease——

Mr. FLOOD. What do you mean by management?

Dr. SHANNON. Management carries the connotation of the administration of both specific and supportive treatment in a time sequence where it is not possible to achieve recovery—and to apply at the bedside the fundamental biological knowledge acquired in basic research programs.

Since 1960 clinical research centers have become an important national resource. There are presently 91 of them in 31 States, the District of Columbia, and Puerto Rico. Sixty-two of the Nation's 94 medical schools are operating clinical research centers, and applications have been submitted or are being prepared by an additional eight schools. This young program has become pivotal to the success of patient-oriented research. Last year, over 1,200 scientific articles were published, reporting new insights into such far-ranging subjects as infant mortality, heart disease, diabetes, cancer, and organ transplantation.

Mr. FLOOD. Why do not all of the medical schools operate clinical research centers?

Dr. SHANNON. Mr. Chairman, I wish some of the schools that are not here had the scientific competence to warrant this type of support, but these clinical research units are made available only in those cases where the scientific competence warrants this very expensive resource.

Mr. FLOOD. Is this a good percentage; 62 out of the 94, is that good?

Dr. SHANNON. I don't believe so, sir; no. I believe there are very few research and teaching enterprises whose educational and service functions could not profit from such units, if they had the scientific talent.

Over 2,700 scientists used these resources and 1,700 medical students and 3,100 physicians received training in research techniques.

### SPECIAL RESEARCH RESOURCES

The special research resources program provides support to enhance the biomedical research capability of the Nation through application of large-scale equipment and instrument-oriented resources to areas of multidisciplinary research endeavor. Many areas of such research (for example, determination of molecular structure or genetic codes) are enormously dependent upon computer resources, specialized instrumentation and/or commercially unobtainable biological materials. Since facilities to fulfill these needs are usually too costly or too expensive in capability to be assigned or managed by a single investigator, a special research resource is established for use by a community of scientists; the basis for organization can be institutional, regional (section, city, State) or national. The Division of Research Facilities and Resources currently supports 51 resources under this program: 42 computer centers, six analytical biochemistry instrumentation resources, and three biomaterial resources.

These resources have participated in an impressive number of significant scientific accomplishments in the past year.

The recent synthesis of DNA by Dr. Arthur Kornberg was materially facilitated by the supply, in reagent quantities, of enzymes essential for the critical experiments.

I will give one example to explain that last term. Many scientists now require the use of biological material, enzyme preparations of specific organic chemicals that are not available from commercial

sources. We set up a limited number of material centers that produce these materials for use by scientists across the Nation. They get better material at a tremendous savings in cost and time.

ANIMAL RESOURCES PROGRAM

The biomedical scientific community continues to require high-quality laboratory animals with known characteristics. The Division of Research Facilities and Resources is meeting some of these needs through support of the National Primate Research Center program and of other animal resource programs.

The seven Primate Research Centers now have their research programs well underway. The normal biology and diseases of many species of nonhuman primates are under investigation. These animals are used as the models most closely resembling the human primate for research in reproductive biology, mental retardation, growth and development, genetics, and the experimental counterparts of human disease.

In addition to primates in medical research, institutions require a large variety of species and strains of laboratory animals of high quality. The animal resources program of DRFR provides assistance to grantee institutions: to establish and maintain colonies of animals particularly essential for research, to conduct research in laboratory animal medicine, to improve the care and welfare of research animals in line with provisions of recent animal care legislation (Public Law 89–544), to investigate new animal models germane to health problems, to operate training programs for the expansion of the pool of competent laboratory animal care experts.

To provide continuing support for these important programs, $67,415,000 is requested. This includes $35,677,000 for the clinical centers, $10,850,000 for the special research resources; $10,500,000 for the primate centers; $5,100,000 for the animal resources and $530,000 for training and fellowship programs related to animal resources; $305,000 for scientific evaluation; and $4,453,000 for direct operations, including collaborative research and development through contracts of scientific communication and information on pharmacology-toxicology, and administrative support for the health research facilities and general research support grants programs. All of these requests are at the same level as in 1968, except for a $5,234,000 increase primarily to meet the burgeoning hospitalization and personnel costs of the clinical centers program, a $12,000 increase to cover increased stipends in the training grants in laboratory animal medicine, and $163,000 increase for direct operations. I shall be happy at this point to answer any questions on this portion of the request.

OFFICE OF INTERNATIONAL RESEARCH

I wish now to address myself to the request for the Office of International Research which has been the focal point in my Office for the administration of the international activities of the National Institutes of Health with responsibility for policy formulation, program analysis, and coordination of activities including liaison with science offices at the State Department and the White House.

The programs of the Office of International Research include: support of five International Centers for Medical Research and Training; the international postdoctoral fellowship program; the international research career development program; the United States-Japan cooperative medical science program; and the special foreign currency program. In addition, the Office of International Research maintains an awareness of the progress of science abroad through a small overseas staff stationed in Paris, Rio de Janeiro, Tokyo, and New Delhi.

The appropriation request for these activities in 1969 is $13,354,000, compared with an operating level of $12,430,000 for 1968. However, with the establishment last year of the John E. Fogarty International Center I am reorganizing the international activities of the National Institutes of Health. This will involve transfer of some functions to the National Institute of Allergy and Infectious Diseases and will require some redistribution of funds and modification of the current budget. This will be done within the funding levels indicated in this statement. I shall submit a proposal on this to the committee shortly. If there are any questions on this section I shall be happy to answer them now.

This is just the rearrangement to provide for the Fogarty Center to take over those things which are appropriate.

### DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

During the past year, the Division of Computer Research and Technology achieved significant growth and a stable, reliable computer facility has emerged. The cost per unit job for computer service and mathematical consultation to NIH staff has been reduced by a third to a half and the number of jobs completed per unit time has risen by seven to 10 times.

The individual and collaborative efforts of the DCRT scientific staff comprise a varied research program. Physical chemical data on the composition and primary structure of the biologically important molecules—the proteins and nucleic acids—are analyzed routinely, using the computer. Our theoreticians have made significant progress in calculating the conformational structure—the three-dimensional structure—of these molecules as a necessary step to understanding how these compounds act in living systems. A rigorous mathematical basis for naming chemical compounds is being sought preliminary to attempting correlation of chemical structure with biological activity.

Clinical data are being evaluated mathematically as part of examining certain physiological properties of the hemodynamics of obstructive heart disease or the demonstration of right or left cerebral dominance on physiological function.

The statisticians are analyzing a vast array of clinical laboratory data to assist the clinical pathologists establish standards and deviations in normal diseased subjects for a host of important clinical laboratory determinations. During the past year, the mathematical, statistical, and data processing needs for a number of epidemiological studies have been satisfied.

This record of activity during the year is not exhaustive, rather it is representative and shows the considerable progress made by the Division.

In support of this program, an increase of $229,000 and seven positions is requested. I shall be happy to answer any questions on this portion of the report.

ENGINEERING DEVELOPMENT

The potential contributions to health and medicine from advances in physical sciences and the application of the principles and practice of engineering sciences to biomedical research and health care give promise of spectacular advances. These contributions can range from development of new, natural, and synthetic materials, sophisticated and miniaturized instrumentation and electronic devices, to computer technology and systems analysis concepts. A critical factor in major program expansion is the determination of when a field or a particular biomedical problem area has reached an optimal point for exploitation.

Developments such as the artificial heart, the artificial kidney, communications systems within particular social settings—for example, hospitals and regional medical programs—make imperative a centralized entity for the effective support and overall guidance of those derivative activities which can be profitably undertaken on a centralized engineering development basis. The NIH, therefore, proposes to initiate action within the funds available to establish a small ongoing unit to provide this direction.

Last year, the NIH negotiated a contract with the National Academy of Engineering for a study of engineering in biology and medicine to assist in our further examination of the potential of this area. The Academy established a Committee on the Interplay of Engineering in Biology and Medicine to examine the future role of engineering concepts and technology in regard to—

Advancing the understanding of biological systems.

Developing research instrumentation, diagnostic and therapeutic devices, and artificial organs.

Designing and developing large-scale systems encompassing major social functions such as health services, as well as their subunits, such as hospitals.

The Academy Committee is also examining the question of how to convert the ill-defined region which lies between engineering and medicine into recognized fields of activity and is now in the process of a detailed study of several institutional complexes involving bioengineering activities which can serve as prototypes for further development of the necessary organizational entities to further this important field.

For the activities in engineering development, we are requesting $1,347,000, including $1 million to initiate contractual support in fields such as instrumentation and artificial internal organ replacement. If there are any questions on this activity, I shall be glad to answer them now.

## THE JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

The Department of Health, Education, and Welfare appropriations bill for fiscal year 1968 included $500,000 in planning funds to construct the John E. Fogarty International Center for Advanced Study in the Health Sciences at the National Institutes of Health as a suitable memorial to the interest and contribution of the late Representative John E. Fogarty to the medical sciences generally and the programs particularly. As you are well aware, the establishment of such a memorial was recommended to the Congress by Representative Melvin Laird of Wisconsin, following Mr. Fogarty's death in January 1967.

Present plans for the new construction authorized for the Fogarty International Center envision a complex of structures on the NIH campus in the proximity of Stone House (building 16) which will be restored to serve as a base for the initiation of the Center. Apart from the long-term utility of this building to the program, its early availability will make it possible to institute a significant part of the Center's program during the fiscal years 1969 and 1970.

Plans for the new Center construction include conference facilities, living quarters for scholars in residence, guest-type rooms for visiting conference participants, food service facilities, lounges, and office space for the Center staff.

The initial function of the Fogarty Center will be to create the environment and provide the means to assemble scholars and scientists capable of original thinking for advanced study of the development of science as it relates to health and its implications and applications for the future.

The interaction resulting from the assembly of outstanding people, working individually, in small groups, or in large conference setting, will, hopefully, yield new findings and concepts which may advance the solution of pressing health problems. A major focus of attention will be on the socioeconomic matrix within which contemporary biomedical science is imbedded. The substance of scientific research will be dealt with both in its practical aspects and in its philosophical considerations.

The development of a well-organized international conference and seminar program centered in the contemporary status of the life sciences, as well as the facilities to house such a program, will be a primary aim of the Center. During the forthcoming year conference programs on the subjects of "The Science Base for Medical Education in the Future," "The Study of Disease in Controlled Populations," and the scientific, legal, and ethical issues of organ transplantation are contemplated.

A scholars in-residence program is also planned for the Fogarty Center. These individuals would concentrate their attention on broad, major problems which have a bearing on the health of society. A major focus of attention will be the assessment of the state of the art

and philosophical and social concepts relative to the thrust of science and its application for human well-being.

Through an international fellowship and exchange program, the Fogarty Center would provide for a new senior scientist exchange program and the existing international postdoctoral fellowship program which will be transferred to the Fogarty Center from the Office of International Research.

The influx of visitors and delegations from foreign countries has become a pressing problem for NIH and has created a crucial need for a reception center. The Fogarty Center will serve as the focal point for reception and guidance of scholars in residence, visiting scientists, and guests. A well-developed reception program would allow us to gain the maximum benefit from foreign scientists visiting the NIH, while at the same time acquainting them with U.S. scientific and cultural facilities.

In order to initiate, on a modest scale, the new programs outlined above and to assemble the necessary staff to operate them, we are requesting $600,000 and 10 new positions in the President's budget for fiscal year 1969. I shall be happy at this point to answer any question on the Fogarty Center.

SUMMARY OF BUDGET

In conclusion, Mr. Chairman, the request for general research and services for 1969 is $87,500,000 compared with an operating level of $79,335,000 in 1968. The total request combines those for the five elements of this appropriation as follows:

| | |
|---|---|
| Division of Research Facilities and Resources | $67,415,000 |
| Office of International Research | 13,354,000 |
| Division of Computer Research and Technology | 4,784,000 |
| Engineering development | 1,347,000 |
| International Center | 600,000 |

We will be glad to answer questions.

JOHN FOGARTY INTERNATIONAL CENTER

Mr. FLOOD. We have already discussed the unfortunate fact that the budget hides the John Fogarty International Center—as a matter of fact, even drops the name. We are very pleased to see your justification material and your affimative statement do not do that.

You said you are asking for $600,000 for the Center, but you didn't say much about what you were going to do with the $600,000. What are you going to do with the money?

Dr. SHANNON. It will pay for the assembly of a staff to conduct the affairs of the Center, to plan it, plan the structure and the program.

We will start the conference program. I mentioned in my justification three areas that are under consideration right now; namely, the science base for medical education in the future, the study of disease in the controlled populations; and three, the scientific, legal and ethical issues of organ transplantation.

These are broad subjects that are not frequently discussed by individual scientists, though they are appreciated. Yet these are some of the very broad issues of today.

Mr. FLOOD. What is the status of your planning for construction? Why haven't you asked for funds for construction?

Dr. SHANNON. The plan for construction is at the stage where the program requirements are essentially completed and will shortly go forward. The program of requirements, which is the first step, is essentially completed now and will go forward.

Mr. FLOOD. How much did NIH ask originally for construction and for operating expenses?

Dr. SHANNON. We have not made a formal request for construction in this budget, primarily because the planning will not be completed within this fiscal year, and we were advised that, with the budget being what it is, it would be more appropriate for construction funds to be requested in the next year so they would be available not long before they are ready for use.

### REQUESTED APPROPRIATION LANGUAGE CHANGE

Mr. FLOOD. Before we talk about dollars, Dr. Shannon, which is one of our great interests here, suppose you tell us what you will do and why it is desirable to do it if you get this new language you are requesting.

Mr. SEGGEL. This is an amendment to section 328 of the PHS act which permits a PHS agency to make a reimbursable agreement with non-Federal organizations to make use of non-Federal medical care facilities and resources. This language would permit the NIH clinical center to enter into such agreements if they need them.

We were told that since this amendment was passed last year we should now incorporate it in our appropriation language. We have been doing this to some extent on a contract basis.

Dr. SHANNON. In the care of a leukemic child, which may involve continuing observation for a period of months, if the child and his mother, for example, are from some distant place, it is to the Federal Government's advantage to be able to house them in a motel rather than to house them in a very costly medical center bed, and be able to pay for it as part of the normal activity.

I might point out that many modern hospitals have been doing precisely this. You provide the resources that are absolutely essential and no more, for the patient. We do not like to use beds supported by very sophisticated setups when they are not required.

Mr. LAIRD. Mr. Chairman, I thought we were doing that.

Mr. FLOOD. So did I.

Mr. SEGGEL. We are doing it by contract. This one provides for sharing medical care facilities and resources in other installations wherever we need to.

Mr. LAIRD. We have had this being done under contract for some period of time. Like the chairman, I wonder just what that language means.

Dr. STEWART. Mr. Chairman, that language is being used wherever we have clinical care facilities. The basic purpose is that if you have patients under care who require a machine or a service or something which may be in community hospital or another hospital, it is more efficient to be able to use that on a reimbursable basis rather than to have to establish it in you own hospital in order to provide the care for the patient.

Dr. SHANNON. Or take the time to set up a contract to permit that.

Dr. STEWART. That was the basic purpose.

Mr. LAIRD. Suppose the child who had leukemia had been out to NIH for a while and then went home. I can how you could use the authority on that basis with some arrangement with a hospital near the home.

Dr. STEWART. That is correct, and in our own Public Health Service hospitals you may have, for example, a kidney machine in a local hospital or a VA hospital where you have an occasional patient, but it isn't worth setting up a new unit within our own hospital. It is that type of exchange that we are talking about.

Dr. SHANNON. In that specific case, we have used the hemodialysis unit in Georgetown but it is a very complicated way of doing it right now.

SUMMARY OF 1969 BUDGET REQUEST

Mr. FLOOD. Your budget for 1968 is $79,335,000 and you are asking $87,500,000. That is an increase of $8,165,000 and 33 jobs.

GENERAL CLINICAL RESEARCH CENTERS

Now, by far the biggest part of this increase, $5,234,000, is for general clinical research centers?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. How much of this is for what you call cost-of-living increases and how much to expand the program?

Dr. SHANNON. I can't give it percentage wise, but roughly 90 percent is the cost-of-living increase.

Mr. SEGGEL. Nearly all is for the increased cost.

Dr. SHANNON. Hospital costs have been going up, as you know, at a rather alarming rate. In these grants for clinical centers, 40 percent of the dollars go into hospital costs and with an increase of hospital costs over the past 2 years at about 15 percent per year, unless that money is provided, we have to cut back the number of beds available.

Mr. FLOOD. How do these centers differ from those funded by your different institutes?

Dr. SHANNON. Some of the institutes, indeed, have clinical centers such as these, where a given project requires beds for a quite narrowly defined project. The Neurological Institute has some, Cancer has some, and so on. But these centers are set up to satisfy the need of an array of individual scientists who are supported in an institution where they do not need any massive bed support, but from time to time will require one, two, or three beds in order to complete their investigation. These centers are operated, generally, under the administration of a bed assignment committee from whom a responsible investigator with a research program can request permission to use one or two or however many bed days are necessary in order to make certain specific observations that are essential for the progress of his work.

As I pointed out, these 91 centers have been used by 1,200 investigators. It is simply a question of good service, excellent service, and economy to provide this type of resource on a centralized basis rather than to try to provide each scientist with money so that he can set up his own little one or two-bed research unit. This provides a basic complement of beds, a basic complement of nursing, diatetic, and laboratory services; a chief who operates this unit, together with an advisory group who allocate the resource. This is probably the only way that much of the present-day highly sophisticated research can be done by individual scientists who have individual grants for their own special purpose.

SPECIAL RESEARCH RESOURCE CENTERS

Mr. FLOOD. You have 51 special research resource centers and most of these are what you call computer centers.

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Now, how did you determine where to locate them, how do you finance them, and how do you administer them?

Dr. SHANNON. This is Dr. Kennedy's specific responsibility.

Dr. KENNEDY. A committee was appointed in about 1960 to explore possible sites for these. It was called the Advisory Committee on Computers in Research, appointed by the Director, NIH. It is made up of consultants from the academic community. For a couple of years they worked to formulate a set of program plans. Since 1962 the center grants have been awarded on the basis of competitive applications, starting with an appropriation in 1962 of $5 million, which has gradually risen to about $9 million.

The computing centers provide essentially two elements: computational services to the community of scholars——

Mr. FLOOD. How do you finance them?

Dr. KENNEDY. We finance them by grants to the university.

Mr. FLOOD. How do you administer them?

Dr. KENNEDY. They are administered by a center director and sometimes an assistant center director whose salaries are funded out of the grant. The grant may pay for the rental charges for the machine; in certain cases the machine is purchased. The grant may also pay for the supporting personnel: mathematicians, computer programers, systems programers and so forth.

Mr. FLOOD. Do you have one in Wisconsin?

Dr. KENNEDY. Well, we have not completely met all of Wisconsin's importunings. We support a center in the medical school there and we have been talking to Wisconson about partial support for their central university computing center.

Dr. SHANNON. There is general agreement among educators and scientists alike that in about 10 years the costs for computation for all purposes will probably amount to as much as 20 percent of the research budget.

Now it is equally apparent that, as we come into this computer age, that the educational system, beginning in high school, but certainly at the collegiate level, must provide training in the use of computational devices.

The Congress made available $20 million this past year to the National Science Foundation in order for them to find out how this tremendous need for computation devices could best be met, stating that they felt that if the Federal Government were, eventually, to support these, it should be part of the Office of Education's normal operational subsidy to institutions of higher education.

In our own case, we are coming to the point where computation devices are being used so extensively that we will have to provide for their cost for individual projects in the research grant. We are considering the establishment of a central unit that will satisfy the needs of a whole institution where the individual scientist will pay for such part of the running time as he uses.

### UNITED STATES-JAPAN COOPERATIVE PROGRAM

Mr. FLOOD. So that we understand the United States-Japan cooperative program a little better, suppose you give us what you call highlights. Last year when we were talking about this, the information you gave us about the Japanese program was a little vague; at least it was to me. What was done under this agreement since we talked about it last year?

Dr. SHANNON. If there is any confusion about this, I would like to submit for the record an insert that gives the history, the dollars spent, and projects undertaken.

Mr. FLOOD. I think that ought to be done.

(The information requested follows:)

REPORT TO CONGRESS PURSUANT TO SECTION 5(h) OF
PUBLIC LAW 86-610 (THE INTERNATIONAL
HEALTH RESEARCH ACT OF 1960)

## U.S.-Japan Cooperative Medical Science Program

### History of the Program

The U.S.-Japan Cooperative Medical Science Program was initiated following a meeting between President Johnson and Prime Minister Sato in January 1965 and at subsequent meetings by the U.S. and Japanese Joint Planning Committee. A mutual endeavor by the two countries to aid all mankind through medical research was determined to be of prime importance, with emphasis being placed in six distinct areas; namely, Parasitic Diseases, Cholera, Virus Diseases, Leprosy, Malnutrition, and Tuberculosis. Although the plan was conceived in 1965, actual award of grants for research in these areas was not accomplished until 1966 (FY 1967). In the relatively short period of time that the program has been active, a significant number of grants have been awarded. In addition, understanding and respect has been attained by the U.S. and Japanese medical research communities, resulting in mutual cooperation toward a common goal. Fruition of these objectives was evidenced at a recent conference where U.S. and Japanese investigators met together outside the formal meetings to individually and constructively criticize one another's work and to exchange both information and materials for evaluation. Thus, the initial steps toward a cooperative undertaking have been achieved in a relatively short period of time. The U.S. and Japanese panels meet at regular

intervals to reconfirm their mutual objectives and make whatever additions or deletions deemed necessary. The present trend is toward meetings of participating nature rather than one of reading scientific papers with little time available for discussions.

During the past year the panel members have succeeded in interesting additional competent scientists to focus their research efforts on the diseases encompassed by this program. The result has been an increase in research grant applications for support of new research projects which hold promise of advancing knowledge in the various disease categories.

In view of the present trends of worldwide travel and the speed by which the travel is accomplished, it becomes increasingly apparent that travelers are exposed to disease and may return to the U.S. while the disease is in a sub-clinical state, thereby exposing others to an infection prior to diagnosis and treatment. Unless decisive steps are taken to counter these factors, the exotic disease of yesterday may become the common threat of today. Japan has begun, as the U.S. has in prior years, to promote medical training, research and medical aid to a number of Asian countries, i.e., their training and diagnostic laboratory for parasitology and virus diseases in Bangkok, Thailand, their anti-leprosy mission in Agra, India, and their clinic and research laboratory at Bandung University, Indonesia to diagnose and treat epidemics occurring in that area.

The Scope of the Program

The scientific program involves the six diseases or disease categories previously mentioned which are prevalent in Asian countries.

The area of Asia considered under this program is not defined rigidly, but may include the Republic of Korea on the north and India and Pakistan on the west, as well as other adjacent countries in the Pacific region.

Primary emphasis is being placed on medical research as the basis for advanced knowledge necessary to effective action. Field research may be undertaken when deemed necessary or desirable. When public health activities become desirable as a result of the joint research program, the Committee may then recommend appropriate methods of implementation.

Organization

The United States and Japanese Governments appointed members to constitute a U.S.-Japan Cooperative Medical Science Committee in 1965. The United States delegation to this Committee is appointed by the Secretary of State for a period not to exceed four years. The delegation, in addition to representing the U.S. at meetings of the Joint Committee, advises the Secretary of State on the scope, direction and other broad aspects of the program and develops plans and proposals to assure that the program meets all the purposes for which it was established. It has designated the six areas of research mentioned above and established Panels in each disease category to implement the research program.

Appointments to Panels have been made by the Director, NIH, each Panel consisting of no more than five members. Consultants may be nominated by each Panel for appointment by the Committee in keeping with the scientific requirements of the Panel.

The United States and Japan maintain separate secretariats. The Office of International Research, National Institutes of Health, functions as the U.S. Secretariat.

Financial Support for the Program

The United States and Japan each support the costs of their own projects and meetings.

The National Institutes of Health, based on the availability of funds and under delegated authority under P.L. 86-610, provides for the support of research projects, is responsible for the organization, funding and conduct of all related scientific meetings held in the United States, and provides and funds the secretariat for the U.S. side.

A Year's Progress

The third joint meeting of the U.S.-Japan Cooperative Medical Science Program was held in Palo Alto, California on July 29, 1967. Again the meeting proved to be most important for the future development of this program. The number of accomplishments and the amount of research undertaken increased noticeably during the second year of the program. These accomplishments were reviewed and plans for the future research efforts of this program were discussed.

Prior to the meeting of the Committee, the joint Panels on Cholera and Parasitic Diseases met and conducted symposia on July 26, 27, and 28, 1967. During these joint meetings reports on the present status of research on these diseases were presented and plans for future activities were discussed. Members of the U.S. and Japanese Delegations attended the joint Panel meetings.

The Chairmen of the U.S. and Japanese Panels on Cholera, Tuberculosis, Leprosy, Parasitic Diseases and Malnutrition presented written and oral

reports to the Joint Committee. The reports described accomplishments since the last Committee meeting and outlined plans in each area for the future. The Chairman of the U.S. Panel on Virus Diseases presented an informal report on the activities of the U.S. Panel. The Joint Committee discussed the reports of the Panel Chairmen and considered the relationship of the proposed projects to the overall objectives of the Cooperative Medical Science Program. After a detailed review of the overall program the committee was unanimous in endorsing the Panel reports. The Committee expressed great satisfaction with the research programs originated under the cooperative program. They were also pleased with the unusually rapid and effective progress of the large number of studies in both the U.S. and Japan.

It should be emphasized that the research efforts of the Cooperative Medical Science Program are only slightly over one year old. The first grants were awarded during the summer of 1966.

Research Highlights of the Past Year

Parasitic Diseases - Both the Japanese and U.S. Panels awarded grants for the study of the biology, physiology, nutrition, biochemistry, epidemiology and genetics of mosquitoes and snails related to the transmission of schistosomiasis and filariasis. The National Institutes of Health has awarded three contracts for the supply of schistosomes, schistosome antigens, and filariids to investigators in the U.S. The Japanese Panel reported materials are being made available through a similar supply to investigators in Japan. This past year's operation has been successful in that new lines of research have been developed

which hold great promise for the control of vectors; newer information was analyzed on the relationships of helminths and vectors and much enthusiasm has been generated which has brought new people into the field of this area of parasitology for both research and training. It is expected that a number of Americans who are interested in insect genetics will begin to devote more attention to problems of filariasis. It is also expected that numerous studies in Japan on insects and snails will be expanded along similar lines. The Japanese Panel has reported on the mechanism of molluscidal action of Yurimin as an uncoupler of oxidative phosphorylation in animal tissue mitochondria. Increased evidence was presented regarding the biologic replacement of disease-carrying mosquitoes by other species as a possible means of control.

Cholera - The primary research goal in cholera research continues to be the development of a vaccine capable of conferring long-term immunity on the great majority of individuals receiving it. The U.S. workers reported the demonstration of high incidence of sub-clinical cholera infection in endemic areas. The development of a canine model which closely simulated human disease is extremely useful for studying and understanding the pathophysiology of cholera. New information from such studies emphasizes the need for continued work designed more precisely to delineate the pathophysiologic mechanism in cholera. The U.S. investigators feel that purification and chemical characterization of the responsible cholera exotoxin will be extremely helpful in this regard and urge continued intensive efforts towards this goal. In light of the past

years clinical studies, additional efforts are being discussed to determine the difference, if any, in pathophysiologic mechanism in adult and pediatric cholera. Studies on the absorptive capacity of the intestinal tract in cholera patients indicate clearly the usefulness of glucose administered orally in therapy. The Japanese workers have reported on studies on the antigenic structure and mutation of cholera vibrio and have made progress in delineating the various sub-types. The promising Japanese studies on sesame oil adjuvant to whole cell vaccine is being vigorously pursued. Their work on isolation and identification of components of cholera vibrio for purposes of immunization is promising. The Japanese have presented excellent work on alteration in structure of cell wall of vibrio cholerae by antibiotics and resistance to commonly used antibacterial drugs. The Joint U.S.-Japan Cholera Panel expressed the hope that WHO would institute a continued surveillance of enteric diseases in south and southeast Asia so the U.S. and Japan Panels could collaborate with advantage, to provide more complete information on the epidemiology of and immunity against cholera.

Malnutrition - The U.S. Malnutrition Panel reported at the end of one year on the research grants and contracts awarded, including a contract to the International Rice Research Institute to facilitate studies to improve the quality and quantity of protein in rice, and a contract to the Massachusetts Institute of Technology for a survey of toxins produced by molds in foodstuffs. Many problems of nutrition are being studied, such as whether there is a relation of malnutrition to mental development, learning and behavior, interactions of malnutrition

and infection, the genetic improvement of the protein content of grains and the procurement of low cost protein foods. The Japanese Panel reported experimental data which show that with lower levels of protein reserve in the body there is higher rate of accumulation of body protein with decreased urinary excretion of riboflavin. A Joint Malnutrition Panel Meeting was held at M.I.T. in December.

Tuberculosis - Since the inception of the U.S.-Japan Cooperative Medical Science Program, the guidelines of the Tuberculosis research program have remained unchanged. Both the Japanese and U.S. investigators agree with the idea that immunologic rather than nutritional or chemotherapeutic tools have the best chance in the long run of being most economically feasible for the control of tuberculosis. The U.S. Panel reported at the end of one year on research grants and contracts awarded. This included the contract for a large supply of B.C.G. organisms which are being made available to American investigators working in immunology. Another contract is being negotiated to supply PPD tuberculin for the same purpose. The Japanese Panel reported on experiments that may be the first step for clarifying our knowledge of tuberculosis infection at the cellular level. Excellent progress is being made in purification of various antigens from mycobacteria. Methods for evaluation of the effects of vaccination have been reported.

Leprosy - The United States Leprosy Panel reported that Mycobacterium leprae is sensitive to unexpectedly small concentrations of the standard therapeutic drug, 4, 4' diaminodiphenylsulfone (DDS), and

that resistance to sulfone treatment by this organism when administered at the recommended dosages is rare, about one in a thousand cases. They also reported evidence that human leprosy, especially the lepromatous type, is usually characterized by a generalized depression of immunity. A striking advance in the experimental study of immunity and treatment has been achieved through the use of infection of the mouse foot-pad with M. leprae. Also it has been found that when thymectomized irradiated mice are inoculated in the foot-pad they develop 10 to 100 times as many bacilli as normal mice do. This development offers interesting new experimental approaches in leprosy research in that now this organism can be cultured in an experimental animal and new and novel techniques may be carried out without the involvement of human patients and the attendant problems associated therewith.

Virus Diseases - The U.S. Panel undertook to implement the four program areas agreed upon at the Honolulu Conference in October 1965. The work which has been supported and undertaken since January 1967 is concerned primarily with the evaluation of vaccines against Japanese B encephalitis; studies on the dengue virus complex, with special reference to hemorrhagic fever; a study of the antigens of rabies virus with the view to developing a more potent vaccine; viral respiratory diseases; and the prophylaxis and treatment of smallpox. In the meantime, to implement the smallpox program, a working conference was held in Honolulu in December 1967. A number of the Japanese colleagues attended to participate along with American investigators.

Research Conferences and Workshops

The United States panels have developed joint conferences with their Japanese counterparts and invited participants as well as special workshops for the American scientists active in the panels' areas. These conferences and workshops are to stimulate and revive interest in the special areas of of the U.S.-Japan Program, to communicate research results, methods and research protocols, and to plan new approaches to help solve the problems that exist in the diseases under study. The list of conferences and workshops for the calendar year follows:

| Date | Conference Title | Sponsoring Panel |
|---|---|---|
| January 27, 1967 | Conference on "The Immunology and Bacteriology of Cholera," Bethesda, Maryland. | Cholera Panel |
| February 6-7, 1967 | Joint Malnutrition Panel Meeting, Tokyo | Joint Malnutrition Panel |
| March 1-3, 1967 | "Malnutrition, Learning, and Behavior," M.I.T., Cambridge, Mass. | Malnutrition Panel |
| May 10-12, 1967 | Leprosy Research Conference and Symposium on Sulfones, San Francisco | Leprosy Panel |
| July 26-28, 1967 | Symposium on Cholera, Palo Alto, California | Cholera Panel |
| July 26-28, 1967 | Symposium on Parasitic Diseases, Palo Alto, California | Parasitic Diseases Panel |
| July 27, 1967 | Joint Cholera Panel Meeting, Palo Alto, California | Parasitic Diseases Panel |
| July 28, 1967 | Joint Parasitic Diseases Panel Meeting, Palo Alto, California | Parasitic Diseases Panel |
| October 17, 1967 | Workshop on "Immunology of Leprosy," Silver Spring, Maryland | Leprosy Panel |

| Date | Conference Title | Sponsoring Panel |
|---|---|---|
| October 18-21, 1967 | Biology of the Mycobacterioses, New York | Tuberculosis and Leprosy Panels |
| October 20, 1967 | Joint Tuberculosis Panel Meeting, New York | Tuberculosis and Leprosy Panels |
| October 21, 1967 | Joint Leprosy Panel Meeting, New York | Tuberculosis and Leprosy Panels |
| December 6-9, 1967 | Working Conference on Smallpox, Honolulu | Virus Diseases Panel |
| December 12-14, 1967 | Symposium on Protein Requirements of Men, M.I.T., Cambridge | Malnutrition Panel |
| December 12-13, 1967 | Joint Malnutrition Panel Meeting, M.I.T., Cambridge | Malnutrition Panel |

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Financing of the Program

In 1968 the funds available for grants are $3,864,000 and for contracts $1,500,000 making a total of $5,364,000. In 1969 an increase of $1,526,000 is requested, all for research grants. If these funds are provided the 1969 total will be $6,890,000 of which $1,500,000 is for contracts and $5,390,000 is for research grants.

Dr. SHANNON. I will now just limit myself to the highlights.

This is an activity established about 2 years ago subsequent to conferences between President Johnson and Prime Minister Sato. It extended a prior agreement between the United States and the Government of Japan covering science generally, in which a small component of the initial agreement covered the medical sciences. It was proposed that a joint committee be set up—I believe five members from the United States, five members from Japan with two cochairmen who would alternate—and, as a result of meetings, they would select certain studies that might be of use to the home country but certainly had a common value for both countries or for a developing country.

As a result of the first conferences, five areas were selected for study, with most of which we ourselves had quite serious concern because of other reasons.

The terms of the agreement were that such work as the United States proposed it would pay for itself. Such work as Japan proposed, it would pay for itself, but by developing the two-country programs in panels that had representation from each country, one would have communality of interest which should facilitate the development of the program and certainly facilitate——

Mr. FLOOD. Are we bound in the way we must spend these funds by any United States-Japan organization?

Dr. SHANNON. No, sir; we are not.

Mr. FLOOD. Then what is the procedure? What is the process for approval of a project?

Dr. SHANNON. The processes for approval of the project are precisely those for the approval of all our other projects. A series of six areas have been selected, parasitic diseases, virus diseases, tuberculosis, leprosy, cholera, and malnutrition. These are all areas we have interest in for other reasons. Within each of these areas, in consultation with the Japanese, we have discussed what we would like to do. They have discussed what they would like to do and then we have provided implementation and integration through joint panels.

Within our own programs the U.S. panel has developed programs in each of these areas.

TUBERCULOSIS

We are not looking at tuberculosis as such. We are specifically looking at that part of the TB problem you discussed with Dr. Davis; namely, the evolution or the development * * *

Mr. FLOOD. Is there a high incidence of TB among the Japanese?

Dr. SHANNON. It is higher than ours.

In this country the conviction is if one is going to eradicate tuberculosis, one has to have an immunizing agent that will produce solid immunity.

Mr. FLOOD. Eradicate tuberculosis?

Dr. SHANNON. Yes. This can be done if it is possible to develop an antigen or vaccine that will produce solid immunity and at the same time not provoke sensitizing reaction.

Mr. FLOOD. I understand tuberculosis is flaring up around the world.

Dr. SHANNON. In some of the developing countries, sir. It is probably one of the more important medical problems of the world.

I was on the WHO Scientific Advisory Committee for 5 years, the initial 5 years of its development. We saw all the work on TB going on throughout the entire world. It was quite easy to reach the conclusion that, even if all of it were quite successful, we would still have tuberculosis as one of the major world problems.

Mr. FLOOD. Has there been a recent flareup in the continental United States?

Dr. SHANNON. I do not really believe so, sir. We do not have it as a major health problem.

Mr. FLOOD. Is it a regional problem?

Dr. SHANNON. It relates to either one of two general problems. One is it occurs in certain individuals who run a very high risk of exposure to it—medical students, hospital workers, nurses, and the like. Also, there are depressed economic areas where there are problems of poor nutrition and poor sanitation, like the Indian population and the Eskimo population.

By and large, this disease is now largely controlled—about as much as it can be short of total immunization.

FUNDING UNITED STATES-JAPAN MEDICAL RESEARCH AGREEMENT

Mr. FLOOD. You are asking $5,390,000 for 1969 for this. How much is Japan spending under this agreement?

Dr. SHANNON. They are not spending nearly as much as we. There are two reasons. This is not an AID-type operation. We are doing this primarily because of our own interests in these major diseases. The unique characteristic of this program, on the other hand, is that the work is done in such a way that there is an extraordinarily intimate contact and collaboration between ourselves and our Japanese colleagues.

Mr. FLOOD. Since you mentioned AID, how much of these funds are spent outside of the United States? Do you have dollars or percentages?

Dr. SHANNON. Very little of this is awarded to grantees outside the United States On the other hand, some of the work is done outside the United States. For example, a grant to the University of St. Louis supports the nutrition program I spoke about this morning, in the villages near Bangkok. This is done by U.S. nationals attached to the University of St. Louis. This is not too different from comparable studies being done in Guatemala. Most of the work on TB—in fact, most of the work in the other areas—is done by U.S. nationals in the United States.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH

Mr. FLOOD. You say—this is your language:

> An intensive review of the international centers for medical research and training has led to the conclusion that the program is maturing.

That is fine. Why should we support it any longer?

Dr. SHANNON. I do not mean mature in the sense that you mean it, sir.

Mr. FLOOD. This is your language and I am curious.

Dr. SHANNON. They have grown up to where they now can be used productively to address ourselves to some very important problems. During the initial years it was quite uncertain whether it would be possible to set up this type of stable, highly sophisticated center overseas so that it could be used to observe biological phenomena in foreign settings and at the same time train young scientists.

I might say that, of the five centers that were set up, we are this year in the process of disassembling one that did not make it.

Mr. FLOOD. The answer to my question was we are using "mature" in a different sense.

Dr. SHANNON. Yes.

JUSTIFICATION MATERIAL

GENERAL RESEARCH AND SERVICES, NATIONAL INSTITUTES OF HEALTH

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation..... | $81,141,000 | $87,500,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate Pos. | 1968 Estimate Amount | 1969 Estimate Pos. | 1969 Estimate Amount | Increase or Decrease Pos. | Increase or Decrease Amount |
|---|---|---|---|---|---|---|---|
| 135 | Division of research facilities and resources..... | 154 | $62,006,000 | 170 | $67,415,000 | +16 | +$5,409,000 |
| 147 | Office of international research..... | 78 | 12,430,000 | 78 | 13,354,000 | -- | +924,000 |
| 156 | Division of computer research and technology..... | 101 | 4,555,000 | 108 | 4,784,000 | +7 | +229,000 |
| 159 | Engineering development | 5 | 344,000 | 5 | 1,347,000 | -- | +1,003,000 |
| 161 | International Center.. | -- | -- | 10 | 600,000 | +10 | +600,000 |
| | Total obligations... | 338 | 79,335,000 | 371 | 87,500,000 | +33 | +8,165,000 |

Obligations by Activity (continued)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Grants: | | | | | | |
| Research | | $64,758,000 | | $70,872,000 | | +$6,114,000 |
| General research support | | (639,000) | | (600,000) | | (-39,000) |
| Scientific evaluation | | (325,000) | | (325,000) | | -- |
| International centers for medical research and training | | (2,800,000) | | (2,300,000) | | (-500,000) |
| General clinical research centers | | (30,443,000) | | (35,677,000) | | (+5,234,000) |
| Special resource centers | | (10,850,000) | | (10,850,000) | | -- |
| Animal resources | | (5,100,000) | | (5,100,000) | | -- |
| Primate centers | | (10,500,000) | | (10,500,000) | | -- |
| Fellowships | | 1,580,000 | | 1,615,000 | | +35,000 |
| Training | | 318,000 | | 326,000 | | +8,000 |
| Direct Operations: | | | | | | |
| Collaborative research and development | 2 | 1,974,000 | 2 | 2,978,000 | -- | +1,004,000 |
| International research | 68 | 3,303,000 | 68 | 3,316,000 | -- | +13,000 |
| International Center | -- | -- | 10 | 600,000 | +10 | +600,000 |
| Computer research and technology | 101 | 4,555,000 | 108 | 4,784,000 | +7 | +229,000 |
| Training activities | 10 | 187,000 | 10 | 187,000 | -- | -- |
| Review and approval of grants | 115 | 1,506,000 | 128 | 1,608,000 | +13 | +102,000 |
| Program direction | 42 | 1,154,000 | 45 | 1,214,000 | +3 | +60,000 |
| Total obligations | 338 | 79,335,000 | 371 | 87,500,000 | +33 | +8,165,000 |
| Unobligated balance, reserve | +11 | 1,806,000 | -- | -- | -11 | -1,806,000 |
| Total, obligations and reserve | 349 | 81,141,000 | 371 | 87,500,000 | +22 | +6,359,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total number of permanent positions..... | 338 | 371 | +33 |
| Full-time equivalent of all other positions..... | 19 | 21 | +2 |
| Average number of all employees..... | 324 | 360 | +36 |
| Personnel compensation: | | | |
| Permanent positions..... | $3,353,000 | $3,629,000 | +$276,000 |
| Positions other than permanent..... | 207,000 | 214,000 | +7,000 |
| Other personnel compensation..... | 9,000 | 10,000 | +1,000 |
| Total personnel compensation..... | 3,569,000 | 3,853,000 | +284,000 |
| Personnel benefits..... | 370,000 | 383,000 | +13,000 |
| Travel and transportation of persons..... | 456,000 | 491,000 | +35,000 |
| Transportation of things..... | 83,000 | 97,000 | +14,000 |
| Rent, communications, and utilities..... | 189,000 | 201,000 | +12,000 |
| Printing and reproduction..... | 125,000 | 157,000 | +32,000 |
| Other services..... | 1,319,000 | 1,523,000 | +204,000 |
| Project contracts..... | 5,576,000 | 6,576,000 | +1,000,000 |
| Payment to "National Institutes of Health management fund"..... | 756,000 | 803,000 | +47,000 |
| Supplies and materials..... | 75,000 | 153,000 | +78,000 |
| Equipment..... | 161,000 | 450,000 | +289,000 |
| Grants, subsidies, and contributions..... | 66,656,000 | 72,813,000 | +6,157,000 |
| Total obligations by object..... | 79,335,000 | 87,500,000 | +8,165,000 |

## Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $81,141,000 |
| Unobligated balance, reserve | -1,806,000 |
| 1968 total estimated obligations | 79,335,000 |
| 1969 estimated obligations | 87,500,000 |
| Total change | +8,165,000 |

| Increases: | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| A. Built-in | | | | |
| 1. Annualization of new positions authorized in 1968 | --- | --- | --- | +$44,000 |
| 2. Annualization of the 1968 pay raise cost | --- | --- | --- | +36,000 |
| 3. One additional day's pay | --- | --- | --- | +8,000 |
| B. Program | | | | |
| 1. Research grants | --- | $64,758,000 | --- | +6,114,000 |
| 2. Fellowships | --- | 1,580,000 | --- | +35,000 |
| 3. Training | --- | 318,000 | --- | +8,000 |
| 4. Collaborative research and development | --- | 1,971,000 | --- | +1,000,000 |
| 5. International center | --- | --- | +10 | +600,000 |
| 6. Computer research and technology | 101 | 4,555,000 | +7 | +186,000 |
| 7. Review and approval | 115 | 1,390,000 | +13 | +67,000 |
| 8. Program direction | 37 | 563,000 | +3 | +20,000 |
| C. Payment to "National Institutes of Health management fund" for centrally furnished services: | | | | |
| 1. Collaborative research and development | --- | 3,000 | --- | +4,000 |

| Increases (cont'd) | Base Positions | Base Amount | Changes from Base Positions | Changes from Base Amount |
|---|---|---|---|---|
| 2. International research... | --- | 129,000 | --- | +1,000 |
| 3. Computer research and technology..... | --- | 149,000 | --- | +2,000 |
| 4. Review and approval..... | --- | 116,000 | --- | +11,000 |
| 5. Program direction..... | --- | 344,000 | --- | +29,000 |
| Total program increases | | | +33 | +8,165,000 |
| Total net change requested..... | | | +33 | +8,165,000 |

Explanation of Changes

Research grants--The increase of $6,114,000 includes $1,419,000 for regular research grants and $5,234,000 for general clinical research centers to support the rising hospitalization costs of the existing centers offset by decreases of $39,000 for general research support grants and $500,000 for International Centers for Medical Research and Training.

Fellowships--$31,000 of the total increase of $35,000 will provide support for 6 added international postdoctoral fellowships for the Office of International Research. The remaining $4,000 will be utilized by the Division of Research Facilities and Resources to cover increased cost of stipends and supply allowances.

Training grants--The increase of $8,000 will provide for the increased cost of stipends.

Collaborative research and development--The program increase of $1,000,000 is to initiate contract efforts toward applying engineering and technological innovations to biomedical problems in the Engineering Development program.

International centers--The $600,000 and 10 positions for this new program will provide for initial establishment costs of the International Center, including the assembly of staff, and for the start of the Scholars-in-Residence program and the International Conference and Seminar program.

Computer research and technology--The increase of $229,000 and 7 positions will provide: additional support for research in and development of original computer systems to monitor critically ill patients, and establish a time shared computer system with optimum capabilities to support the medical management functions required in the operation of a large research hospital.

Explanation of Changes--Continued

Review and approval--The program increase of $67,000 and 13 positions are required for the scientific administration of the several grant programs, and for the processing and fiscal management of grants.

Program direction--The increase of $20,000 and three positions will provide additional staff required for overall administration, planning and evaluation.

## Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act<br>Section 301--Research and Investigation, in general..... | Indefinite |

PUBLIC HEALTH SERVICE ACT

Title III -- General Powers and Duties of Public Health Service

PART A -- RESEARCH AND INVESTIGATION

In General

"Sec. 301. The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, seqage treatment, and pollution of lakes and streams. In carrying out the foregoing the Surgeon General is authorized to--.....

(c) Establish and maintain research fellowships in the Service with such stipends and allowances, including traveling and subsistence expenses, as he may deem necessary to procure the assistance of the most brilliant and promising research fellows from the United States and abroad;

(d) Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research or research training projects as are recommended by the National Advisory Health Council ....."

Justification

GENERAL RESEARCH AND SERVICES

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits | 338 | $3,939,000 | 371 | $4,236,000 | 33 | +$297,000 |
| Other expenses | ... | 75,396,000 | ... | 83,264,000 | .. | +7,868,000 |
| Total | 338 | 79,335,000 | 371 | 87,500,000 | 33 | +8,165,000 |

General Statement

The appropriation for General Research and Services finances the Division of Research Facilities and Resources, the Office of International Research, the Division of Computer Research and Technology, the Engineering Development activity, and the International Center for Advanced Study in the Health Sciences. Each of these is described individually in the following justification.

Division of Research Facilities and Resources

Obligations by Activity

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Grants: | | | | | | |
| Research | | $57,198,000 | | $62,432,000 | | +$5,234,000 |
| General clinical research centers | | (30,443,000) | | (35,677,000) | | (+5,234,000) |
| Scientific evaluation | | (305,000) | | (305,000) | | (0) |
| Special research resources | | (10,850,000) | | (10,850,000) | | (0) |
| Animal resources | | (5,100,000) | | (5,100,000) | | (0) |
| Primate centers | | (10,500,000) | | (10,500,000) | | (0) |
| Fellowships | | 200,000 | | 204,000 | | +4,000 |
| Training | | 318,000 | | 326,000 | | +8,000 |
| Direct operations: | | | | | | |
| Collaborative research and development | 2 | 1,974,000 | 2 | 1,978,000 | -- | +4,000 |
| Review and approval of grants | 115 | 1,506,000 | 128 | 1,608,000 | +13 | +102,000 |
| Program direction | 37 | 810,000 | 40 | 867,000 | +3 | +57,000 |
| Total obligations | 154 | 62,006,000 | 170 | 67,415,000 | +16 | +5,409,000 |
| Unobligated balance reserve | 4 | 8,000 | -- | -- | -4 | -8,000 |
| Total, obligations and reserve | 158 | 62,014,000 | 170 | 67,415,000 | +12 | +5,401,000 |

Division of Research Facilities and Resources

Research Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| General clinical research centers | $30,443,000 | $35,677,000 | +$5,234,000 |
| Scientific evaluation | 305,000 | 305,000 | 0 |
| Special research resources | 10,850,000 | 10,850,000 | 0 |
| Animal resources | 5,100,000 | 5,100,000 | 0 |
| Primate centers | 10,500,000 | 10,500,000 | 0 |
| Total research grants | 57,198,000 | 62,432,000 | +5,234,000 |

Introduction:

The primary mission of the Division of Research Facilities and Resources is to provide the Nation's scientific community with the resources and the research facilities essential for sustaining and advancing the National biomedical research and research training program. The Division's programs underpin a broad spectrum of science by supporting services that are essential to the total panorama of biomedical research activities.

The programs administered by the Division provide support for clinical research centers where physicians and scientists can study human disease; for computer centers and other special research resources that form a most important technological base for modern research; for critically important laboratory animal facilities and resources essential to a wide variety of specialized biomedical research efforts; and for several other types of major biomedical research resources.

General Clinical Research Centers

The clinical centers provide the facilities and resources in which the Nation's clinical investigators can study human diseases to increase the understanding of the nature and natural history of disease; to extend the capability of medical science; to treat and manage disease; and to apply at the bedside the fundamental biological knowledge acquired in basic research programs.

Each center is a physically discrete research ward where scientists from many disciplines work together carrying out intensive, exacting research and typically consists of eight to thirty beds; a staff of nurses and technicians; a complement of laboratories and other supporting facilities. Research at these centers include major disease areas such as cancer, cardiovascular rena;-diseases, infectious diseases, organ transplantation, the process of aging and diseases contributing to high infant mortality rates.

Program plans in 1968 and 1969

The $30,443,000 available in 1968 for the General Clinical Research Centers program will provide support for the existing program. This includes at this time 91 centers. The $35,677,000 requested for 1969 will provide continuing support for the program. A large portion of the increase of the $5,234,000 will be used to meet the sharply rising costs of hospitalization and wages in existing centers. Such medical costs have been escalating at a rate substantially greater than the increase in costs in other areas of the economy. As these items comprise the major portion of support funds, it is vital that provisions be made to meet such funding needs if the centers are to continue at an effective operating level. In addition, if funding permits, new centers will be established in institutions whose applications have been adjudged worthy by the peer review system.

The following are a few of the many projects conducted in General Clinical Research Centers during the past year:

Metabolism during starvation: Following the first 48-hour period of complete starvation the body depends primarily upon metabolism of broken down fat stores to meet its energy requirements. The source of energy for brain metabolism during starvation has been an unresolved mystery because it has always been thought that the brain depends exclusively upon glucose for energy, and the amount of glucose available falls markedly during prolonged fasting. Scientists at Peter Bent Brigham Hospital have demonstrated that the brain develops the ability to metabolize certain fat breakdown products during starvation, and moreover, that cerebral function is completely normal during this period. These findings have great significance for human medicine, but also are of importance in other areas of human stress. In prolonged space flight, for example, it would be possible for an individual with good fat stores to survive for many weeks on no caloric intake without impairment of cerebral function.

Skin disease: Patients with extensive psoriasis, a skin disease affecting five to ten million people in the United States, have been investigated in the Clinical Research Center at The Mount Sinai Hospital in New York. Dramatic improvement in the disease has been obtained in most patients through the use of a diet poor in tryptophan, an amino acid found in many varieties of foodstuffs. These studies are being continued in the center utilizing carefully formulated controls. It is hoped that by dietary manipulations such as this or similar ones, cures may be obtained in a large portion of patients suffering from this disease.

Infant mortality: Infants born without the thymus gland suffer from recurrent, disabling infections, do not grow normally, and usually die at a young age. Research workers at the University of Miami have successfully transplanted a thymus gland from an aborted fetus to an infant born without 2 thymus gland. Subsequent to this operation, the infant has had no more infections, he has begun to thrive physically, and immunologic tests performed

serially have pointed toward persistently normal thymus function.

Cancer: Although several types of drugs are available for the treatment of inoperable breast cancer, there is no accurate means of predicting in advance which drug will be the most effective choice in an individual patient and the physician must often wait weeks to months to determine the effectiveness of the drug selected.

Research workers in the General Clinical Research Center at Jefferson Medical College have developed a heat-sensitive electronic detector system which continuously records temperatures over tumor and normal breast tissue. Changes in metabolic activity due to drug therapy have been demonstrated, and this promises to be a useful technique both in selection of the most appropriate drug for a particular patient and in investigation of the effectiveness of new antitumor drugs.

High blood pressure: Among patients with lifelong high blood pressure, a group was found by workers at the University of California's Clinical Research Center at the San Francisco General Hospital to have markedly increased production of several hormones secreted by the adrenal gland due to excessive output of ACTH (adrenocorticotropin) from the pituitary gland. The production of these hormones was then blocked by administration of similarly structured natural hormones, with complete cure of the hypertensive condition. As a result of this discovery patients with previously severe high blood pressure and serious disability have been able to resume active lives.

## Scientific Evaluation

The $305,000 requested for 1969 will support the study sections, and preliminary review committees used by the Division to provide scientific merit review of grant applications.

These study sections and committees, composed of outstanding authorities in the various fields of medical research, are responsible for the scientific peer evaluation of all research grant applications and

their recommendations are provided to the appropriate National Advisory Council.

Special Research Resources

This program provides support to enhance the biomedical research capability of the nation through applications of large scale equipment and instrument-oriented resources to areas of multidisciplinary research endeavor. Many areas of such research (such as determination of molecular structure or genetic codes) are substantially dependent upon computer resources, specialized instrumentation and/or commercially unobtainable biological materials. Since facilities to fulfill these needs are usually too costly or too extensive in capability to be assigned or managed by a single investigator, a Special Research Resource is established for use by a community of scientists; the basis for organization can be institutional, regional (city, state, section), or national. The needs of universities, hospitals, and other institutions for computer resources and centralized instrumentation facilities, for laboratories devoted to large-scale preparation of commercially unavailable biological materials, and other Special Research Resources is growing rapidly as the sophistication, capabilities, and costs of modern research increases. The progressive quantification of the biological sciences is reflected in the increasing requirements for specialized equipment, such as computers and analytic biochemistry instruments. Computing devices have served biomedical research not only in mathematical and statistical applications but also in process control functions where the experimental procedures themselves as well as the data are monitored and modified automatically.

Closely associated with instrumentation per se is the dependence upon continuing progress in the design of new instruments and the development of new applications and modifications of existing ones. The recognition of a need for new instruments and applications does not generally occur without an interdisciplinary effort involving biological scientists, physical scientists, and engineers. The opportunities for such interactions are by no means common in most biomedical research institutions. However, the necessary collaborative efforts are aided considerably by the mechanism of research resources devoted to the problems of biomedical instrumentation.

Program plans in 1968 and 1969

The $10,850,000 available in 1968 will provide support for a program currently composed of 51 centralized resources of which 42 are computer centers, six analytical biochemistry instrumentation resources and three biomaterials and information sciences resources. The same amount requested for 1969 will provide continuing support for the program.

Animal Resources

The rapid growth of biomedical research has imposed a substantial requirements for laboratory animal resources which will provide animals of the quality and the quantity needed for all branches of specialized medical research. In addition, certain species of animals are becoming increasingly important for the development of model systems and continued

efforts will have to be made to provide such animals, properly conditioned and in sufficient numbers, for this type of experimental use.

Of great importance is a program of grants in the special field of laboratory medicine to provide important data and information concerning the major animal diseases. Such research grants will focus increasingly on improving the health of laboratory animals needed for medical research and research training. Included in the research program would be the acquisition of biomedical and physiological data on laboratory animals, both in normal and diseased states and under various environmental influences. This information provides essential background information to the research worker and also provides the basis for improved standards of animal care.

Of equal importance is the need in the laboratory animal field to strengthen institutional laboratory animal resources. Demands made on animal resources by basic and programmed research and the national concern that research animals be given optimal care at all times make it imperative that all institutions engaged in medical research have adequate programs of research animal care. Grants will be made to assist in the initiation of such programs by providing for certain renovations, key personnel, and for specialized equipment such as animal surgery equipment, anesthesia machines and cage cleaning machines. Diagnostic laboratories to provide early detection of animal diseases and identification of inapparent infections which are disastrous to research studies are necessary to any good institutional animal resource program.

Program plans in 1968 and 1969:

The $5,100,000 available in 1968 will provide support for a program currently consisting of 34 ongoing resources and enable the establishment of about 23 new ones.

The passage of PL 89-544 in 1966 provided that certain animals be provided humane care and treatment. The impact of this requirement is now becoming evident in the increasing requests from institutions for equipment and extensive renovation. The $5,100,000 requested for 1969 will provide support for a program expected to include 45 continuations and an estimated 20 new grants for animal resources, including renovation of institutional facilities to meet the new standards.

## Primate Centers

The primate centers are a unique resource which provide support for facilities, animals, and research so that resident and visiting scientists can perform studies with non-human primates. Research on primates in many respects most nearly approximates carrying out studies in man and is invaluable as a prelude to clinical investigations. Such studies require the maintenence of large numbers of primates under laboratory conditions.

The program for primate centers was established by Congress in 1959 to provide optimal facilities and environment in which resident and visiting scientists of many disciplines could conduct research on those human health problems that could be studied by utilizing the subhuman primates as the biological model.

Significant accomplishments have already been realized in infectious disease studies, reproduction and population control, and mental retardation, to name only a few. Equally important is the rapidity with which information on the colonization, breeding and maintenance of the primates in a research environment is being accumulated and disseminated. In addition, this program is providing previously unavailable leadership in the development of institutional primate resources for support of medical research.

Program plans in 1968 and 1969:

Since the construction of the six regional centers and one national center has now been completed, the $10,500,000 requested will provide continuing support for operation of the seven primate centers. The ongoing programs include the establishment of methods of breeding and of maintaining healthy stocks of non-human primates of all ages over long periods of time; the determination of the suitability of various species for different kinds of investigations; and the continuing evolution of the proper research resources environment to undertake these studies.

Plans for 1968 and 1969 provide for continuing support of the seven primate centers as follows:

| | 1968 Estimate | 1969 Estimate |
|---|---|---|
| Regional Primate Research Centers: | | |
| 1. Medical Res. Found. of Oregon Portland, Oregon | $1,850,000 | $1,850,000 |
| 2. University of Washington Seattle, Washington | 1,350,000 | 1,350,000 |
| 3. University of Wisconsin Madison, Wisconsin | 1,700,000 | 1,700,000 |
| 4. Emory University Atlanta, Georgia | 1,400,000 | 1,400,000 |
| 5. Tulane University New Orleans, Louisiana | 1,450,000 | 1,450,000 |
| 6. Harvard University Boston, Massachusetts | 1,350,000 | 1,350,000 |
| National Center for Primate Biology: | | |
| 7. University of California Davis, California | 1,400,000 | 1,400,000 |
| Total | 10,500,000 | 10,500,000 |

## Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total fellowships..... | $200,000 | $204,000 | +$4,000 |

Introduction:

At the present time, numbers of individuals trained in laboratory animal science and medicine are inadequate for the needs of the biomedical science research community. Under this program scientists with demonstrated ability in such areas as the laboratory animal sciences will be able to pursue special problems in experimental anesthesiology, pathology, virology, primatology, biochemistry, in order to meet the needs in this expanding field.

Program plans in 1968 and 1969:

The $200,000 available in 1968 will provide support for 20 fellowships at the postdoctoral level. The $204,000 requested for 1969 will provide support for the 13 continuing fellowships and seven new fellowships.

## Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting..... | 4 | $41,000 | 13 | $130,000 | +9 | +$89,000 |
| 2. New..... | 16 | 159,000 | 7 | 74,000 | -9 | -85,000 |
| 3. Total fellowships..... | 20 | 200,000 | 20 | 204,000 | -- | +4,000 |

## Fellowships (by type of program)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Postdoctoral..... | 13 | $119,000 | 12 | $125,000 | -1 | +$6,000 |
| 2. Special..... | 7 | 81,000 | 8 | 79,000 | +1 | -2,000 |
| 3. Total fellowships..... | 20 | 200,000 | 20 | 204,000 | -- | +4,000 |

Training Grants

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Total training grants.... | $318,000 | $326,000 | +$8,000 |

Introduction:

The increased use of animals in medical research programs, not only in total numbers, but also in the variety of species, and the necessity of using animals raised under controlled conditions, have resulted in a great demand by medical research institutions for professional support by specialists in laboratory animal medicine.

Program plans in 1968 and 1969:

The $318,000 available in 1968 will provide for seven training grants at the graduate level in the field of laboratory animal medicine. The $326,000 requested in 1969 will continue the seven current grants.

The program will include graduate training in pathology, microbiology, surgery, physiology, genetics, and other fields related to laboratory animals.

Distribution of Training Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| Graduate | No. | Amount | No. | Amount | No. | Amount |
| 1. Continuations: | | | | | | |
| a. Noncompeting.... | 4 | $197,000 | 7 | $326,000 | +3 | +$129,000 |
| b. Competing..... | 2 | 90,000 | - | -- | -2 | -90,000 |
| 2. New..... | 1 | 31,000 | - | -- | -1 | -31,000 |
| 3. Total training grants | 7 | 318,000 | 7 | 326,000 | 0 | +8,000 |

Collaborative Research and Development

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 2 | $29,000 | 2 | $31,000 | -- | +$2,000 |
| Other expenses..... | | 1,945,000 | | 1,947,000 | | +2,000 |
| Total..... | 2 | 1,974,000 | 2 | 1,978,000 | -- | +4,000 |

This activity supports studies carried out primarily through research contracts with industry, universities and other Federal and non-Federal institutions.

Program plans in 1968 and 1969

The funds available in 1968 and 1969 will be used to provide contracts in the areas of pharmacology-toxicology, special research resources and laboratory animal care.

Contracts for pharmacology-toxicology will be used primarily for the development of computer-based techniques for manipulating chemical and biological information so as to accelerate the realization of systems for handling numerical and other data related to the interactions between living systems and exogenous drugs and poisons, as well as endogenous chemical compunds. Such efforts will include development of an adequate body of test data on compounds which have fairly specific biological effects and computer techniques designed to manipulate and process large files of pharmacological information.

The increase of $4,000 is for centrally furnished services from the "National Institutes of Health management fund".

Review and Approval of Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 115 | $1,222,000 | 128 | $1,290,000 | +13 | +$68,000 |
| Other expenses..... | | 284,000 | | 318,000 | | +34,000 |
| Total..... | 115 | 1,506,000 | 128 | 1,608,000 | +13 | +102,000 |

This activity supports the scientific and administrative staff of the Division's special research grant programs, General Research Support programs and the Health Research Facilities construction program. This includes program planning and development; review and evaluation of grant applications for presentation to the National Advisory Research Resources Council, the National Advisory Council on Health Research Facilities and the National Advisory Health Council. Other duties of this activity include liaison with applicants, grantees, other components of the NIH, the PHS, advisory bodies, and interested organizations.

The increase requested will provide 13 positions and $67,000 for assistance in program management.

Included in the net increase are mandatory increases of $8,000 for the annualization of new positions in 1968, $4,000 for one additional day's pay in 1969 and $12,000 for annualization of the 1968 pay raise costs. There are also increases of $11,000 for centrally furnished services from the "National Institutes of Health management fund".

## Program Direction

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 37 | $435,000 | 40 | $456,000 | +3 | +$21,000 |
| Other expenses..... | | 375,000 | | 411,000 | | +36,000 |
| Total..... | 37 | 810,000 | 40 | 867,000 | +3 | +57,000 |

This activity is responsible for the overall direction, administration, planning, evaluation and data analysis of the several programs of the Division of Research Facilities and Resources. The requested program increase of $20,000 will be used for increased operating costs and support of three positions for program administration.

Included in the net increase are mandatory increases of $5,000 for the annualization of new positions in 1968, $2,000 for one additional day's pay in 1969 and $3,000 for annualization of the 1968 pay raise costs. There is also an increase of $27,000 for centrally furnished services from the "National Institutes of Health management fund".

Office of International Research

Obligations by Activity

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Grants: | | | | | | |
| Research | | $7,560,000 | | $8,440,000 | | +$880,000 |
| General Research Support | | (639,000) | | (600,000) | | (-39,000) |
| Scientific Evaluation | | (20,000) | | (20,000) | | -- |
| International Centers for Medical Research and Training | | (2,800,000) | | (2,300,000) | | (-500,000) |
| Fellowships (International Postdoctoral) | | 1,380,000 | | 1,411,000 | | +31,000 |
| Direct Operations: | | | | | | |
| International Research | 68 | 3,303,000 | 68 | 3,316,000 | -- | +13,000 |
| Training Activities | 10 | 187,000 | 10 | 187,000 | -- | -- |
| Total obligations | 78 | 12,430,000 | 78 | 13,354,000 | -- | +924,000 |
| Unobligated balance reserve | 3 | 1,675,000 | -- | -- | -3 | -1,675,000 |
| Total obligations and reserve | 81 | 14,105,000 | 78 | 13,354,000 | -3 | -751,000 |

| | Research Grants | | |
|---|---|---|---|
| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
| Regular Projects | $4,101,000 | $5,520,000 | +$1,419,000 |
| Special Program | 3,459,000 | 2,920,000 | -539,000 |
| Total research grants | 7,560,000 | 8,440,000 | +880,000 |

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Research Project Grants to Former International Postdoctoral Fellows..... | $237,000 | $130,000 | -$107,000 |

Introduction

This program has been designed to facilitate optimum utilization of research training received in the United States by promising young foreign biomedical investigators previously supported by NIH international Postdoctoral Fellowships. The program provides some of the resources needed by these highly talented and carefully selected individuals in commencing independent research careers in their home countries. The applications for modest research project grants, limited ordinarily to $2,500 for each of three years and not renewable, receive careful review by both the International Fellowship Review Panel and the National Advisory Health Council. The grants usually provide for sub-professional technical assistance, equipment and supplies, and serve not only to protect the training investment made in the foreign scientist by encouraging the inauguaration of his independent research career on return to the home country, but also to stimulate continuation and development of a productive collaborative relationship begun earlier between the Fellow and his American preceptor. In many cases, Fellows develop a fresh interest in problems which are of pressing and immediate concern to the health of the American people and are strongly motivated to continue efforts along these lines following completion of their training in the United States. These grants promote such efforts. Furthermore it is becoming increasingly clear that progress in the health sciences recognizes no national boundaries, and all nations share in the afflictions common to all and therefore as a matter of self-interest are compelled to show concern for and activities directed toward solution of common health problems. This program, along with the international fellowship program supports research and training in all the related sciences ranging from heart disease to cancer, chronic infectious diseases, nutritional and metabolic problems, epidemiology of mental and behavioral disorders, development of new surgical techniques, understanding of the genetic basis for health and development, and community and environmental health problems.

Program Plans in 1968 and 1969

The mode of support for former fellows is under study. Commitments made in 1967 or earlier for three-year periods will be honored. To fulfill these commitments, we plan to make 94 awards for $237,000 in 1968 and 52 awards for $130,000 in 1969.

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Research Project Grants (U.S. Japan Program)..... | $3,864,000 | $5,390,000 | +$1,526,000 |

Introduction

In 1966 President Johnson and Prime Minister Sato, mindful of the many areas of human health which are of mutual concern to the peoples of the U.S. and Japan agreed to undertake a greatly expanded program of cooperation in medical science. As a first step to implement this agreement, they agreed to convene a conference of the foremost medical scientists from the United States and Japan to work out the details of the new program. The U.S.-Japanese Joint Planning Committee held a planning conference in Tokyo. This was followed by a Joint Committee Meeting in Honolulu during August 17-19, 1966.

The program is concerned with the diseases of mutual importance to the health of the peoples of the U.S. and Japan. These diseases or categories of diseases include: cholera, tuberculosis, leprosy, virus diseases (arbovirus, respiratory virus, smallpox, and rabies), parasitic diseases (schistosomiasis and filariasis), and malnutrition.

Primary emphasis is placed on medical research as the basis for advanced knowledge necessary to effective action. Field research may be undertaken when deemed necessary or desirable but primary emphasis is on laboratory research.

The United States and Japanese Governments have appointed members to constitute a U.S.-Japan Cooperative Medical Science Committee. The United States delegation to this Committee is appointed by the Secretary of State for a period not to exceed four years. The delegation, in addition to representing the U.S. at meetings of the Joint Committee, advises the Secretary of State on the scope, direction and other broad aspects of the program and develops plans and proposals to assure that the program meets all the purposes for which it was established. It has designated the six areas of research mentioned above and established Panels in each disease category to implement the research program.

Appointments to Panels have been made by the Director, NIH, and each Panel consists of five members. Consultants may be nominated by each Panel for appointment by the Committee in keeping with the scientific requirements.

The United States and Japan maintain separate secretariats. The Office of International Research, National Institutes of Health, functions as the U. S. secretariat.

The United States and Japan share the costs of the program. Projects of U.S. scientists are supported by the United States and those of the Japanese scientists by Japan.

The National Institutes of Health, based on the availability of funds and delegated authority under P.L. 86-610, provides for the support of scientific projects, is responsible for the organization, funding, and conduct of all scientific meetings held in the United States, provides financial support to the United States Panel members, consultants for attendance at meetings related to the U.S.-Japan Cooperative Medical Science Program, and provides and funds the U. S. secretariat.

Program Plans in 1968 and 1969

The allowance of $3,864,000 for grants in 1968 will provide for approximately 88 research grants in the areas of cholera, leprosy, tuberculosis, virus diseases, infectious diseases and malnutrition. The requested amount of $5,390,000 in 1969 will provide for the continuation of 86 of these research grants and the provision for about 36 new and competing continuation research project grants.

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| | 1968 Estimates | 1969 Estimates | Increase or Decrease |
|---|---|---|---|
| International Centers for Medical Research and Training..... | $2,800,000 | $2,300,000 | -$500,000 |

Introduction

International Centers for Medical Research and Training (ICMRT) promote collaborative research and research training between U. S. universities and selected foreign institutions and investigators. Five International Centers now in operation provide unusual field experience and exceptional biomedical research opportunities for American physicians and scientists. These university-sponsored Centers derive their financial support from research grants awarded by the National Institutes of Health. The five universities and their overseas affiliates are as follows:

| United States University | Foreign Affiliate Institution |
|---|---|
| Johns Hopkins University | All India Institute of Hygiene and Public Health and the Calcutta School of Tropical Medicine, Calcutta, India |

| United States University | Foreign Affiliate Institution |
|---|---|
| University of California | Institute for Medical Research, Kuala Lumpur, Malaysia, and the University of Malaya, Singapore |
| Tulane University | Universidad del Valle, Cali, Colombia |
| Louisiana State University | University of Costa Rica, San Jose, C. R. |
| University of Maryland | Institute of Hygiene and Lahore General Hospital, Lahore, W. Pakistan |

Program Plans in 1968 and 1969

Further efforts to involve a greater number of scientific disciplines of the grantee institutions in the existing ICMRT's is underway. Program Directors have been encouraged to broaden their programs whenever possible through additional health-related research projects mounted upon ICMRT administrative structure, but financed by private foundations, by other federal agencies or by means of independent NIH grant awards to individual university investigators for discrete, well-defined investigations. Therefore, a variety of projects, other than those discussed, are being undertaken at the ICMRT sites. Other sources of participation and subsidy may thus contribute substantially to the development of comprehensive, multidisciplinary programs for the study of all health problems, as well as those devoted to medicine in the tropics. A continuing review of their scientific accomplishments and future programming is made by the Committee on International Research. It is apparent through review that these ICMRT organizations are now providing for American scientists research and training opportunities which cannot be duplicated in the United States. An intensive review of the programs in each center has led to the conclusion that the program is maturing. The support given in the past was intended for stimulation which would ultimately develop into an autonomous operation by the university. Critical review of the present operation has developed recommendations toward this objective.

Distribution of Research Grants

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 1. Non-Competing Continuations..... | 146 | $2,493,000 | 141 | $3,912,000 | -5 | +$1,419,000 |
| 2. Competing projects.. | 36 | 1,467,000 | 36 | 1,467,000 | -- | -- |
| 3. Supplementals..... | (20) | 141,000 | (20) | 141,000 | -- | -- |
| 4. Subtotal, regular... | 182 | 4,101,000 | 177 | 5,520,000 | -5 | +1,419,000 |

Distribution of Research Grants (cont'd)

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| 5. General research support grants.... | -- | 639,000 | -- | 600,000 | -- | -39,000 |
| 6. Scientific evaluation | -- | 20,000 | -- | 20,000 | -- | -- |
| 7. ICMRT..... | -- | 2,800,000 | -- | 2,300,000 | -- | -500,000 |
| 8. Total, research grants..... | 182 | 7,560,000 | 177 | 8,440,000 | -5 | +880,000 |

## Fellowships

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| Fellowships (International Postdoctoral)..... | $1,380,000 | $1,411,000 | +$31,000 |

Introduction

The International Postdoctoral Fellowships Program offers a unique opportunity for the sharing of scientific information on an international basis by permitting foreign investigators to work for a period of a year or two in collaboration with, and in the laboratories of, American colleagues in the United States. This program provides U. S. scientists access to the ideas of vigorous young investigators with stimulating and different viewpoints. In addition, since Fellows return to do independent research in their home countries, a basis is provided for the future collaboration between investigators here and those in different environmental settings.

Program Plans in 1968 and 1969

This program will be continued in 44 countries in 1969. Each country, through a nominating committee composed of prominent scientists of that country, submits its recommendations for fellowships. These nominations are competitively reviewed by the International Fellowship Review Committee at the NIH. On the advice of the International Fellowship Review Committee the period of fellowships support has been lengthened to two full years.

It was pointed out by the Committee that a fellow has his most productive time on the project during the second year. The additional funds requested for this program will provide for about 6 more continuations in 1969 while keeping the number of new Fellows at a constant level.

Distribution of Fellowships

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount |
| Continuations (Non-competing)..... | 63 | $401,000 | 69 | $432,000 | +6 | +$31,000 |
| New Fellowships..... | 100 | 979,000 | 100 | 979,000 | -- | -- |
| Total Fellowships..... | 163 | 1,380,000 | 169 | 1,411,000 | +6 | +31,000 |

International Research

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 68 | $969,000 | 68 | $981,000 | -- | +$12,000 |
| Other expenses..... | -- | 2,334,000 | -- | 2,335,000 | -- | +1,000 |
| Total..... | 68 | 3,303,000 | 68 | 3,316,000 | -- | +13,000 |

Introduction

The Office of International Research is responsible for coordination, policy formulation, and analysis of the National Institutes of Health International programs and activities. Included are responsibilities for administration of the U.S.-Japan Cooperative Medical Science Program, the NIH Special Foreign Currency Program, International Centers for Medical Research and Training Grants, Visiting Scientists Program, International Postdoctoral Fellowships Program, International Research Career Development Program, and Overseas Offices located in Rio de Janeiro, Brazil; Paris, France; Tokyo, Japan; and New Delhi, India.

Program Plans in 1968 and 1969

In 1968 and 1969 it is planned to continue operations of the international programs listed above at approximately the same levels.

This request will provide funds for review and approval of international Postdoctoral Fellowships, Project Research Grants for Returning International Fellows, and special grants for International Centers for Medical Research and Training. This activity supports the review and advisory committee evaluating these grants and fellowships, and the staff which analyzes, processes and manages the grants and fellowships.

The request also supports the activities of NIH offices at four overseas locations: Paris, Rio de Janeiro, Tokyo and New Delhi. The four overseas offices provide information on scientific interests, capabilities and resources abroad and make recommendations on NIH policy and program development. They provide basic information which is used by the analytic activity next described.

Support is also provided for an analytic activity which advises NIH management and the several Institutes on the extent, scope, and direction of scientific programs in relation to activities abroad. This activity also collates information on medical research efforts of other countries so that program decisions can take account of these efforts.

The request also provides for staff to operate and coordinate the NIH program utilizing U.S. owned foreign currency (P.L. 480 program).

The request also provides funds for contracts, staff support, and conferences for the U.S.-Japan Cooperative Medical Science Program. Contracts provide for directed scientific effort in the areas of cholera, leprosy, tuberculosis, parasitic diseases, virus diseases and malnutrition. Conferences and workshops to stimulate both program and scientific progress in these areas are also supported.

Both Japanese and American scientists provide scientific leads and ideas to each other, which are immediately acted upon in their own research projects.

The increase of $13,000 which is requested includes $10,000 for annualization of pay raises in 1968, and $2,000 for one more day of pay in 1969, and $1,000 for centrally furnished services from the "National Institutes of Health management fund."

Training Activities

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 10 | $120,000 | 10 | $120,000 | -- | -- |
| Other expenses..... | -- | 67,000 | -- | 67,000 | -- | -- |
| Total..... | 10 | 187,000 | 10 | 187,000 | -- | -- |

Introduction

The International Research Career Development Program (IRCDP) was started in Fiscal Year 1963 by the National Institutes of Health to develop competence in the Public Health Service in medical research related to problems of an international nature which cannot ordinarily be undertaken in the United States and to provide opportunities for promising young scientists to work abroad as members of the U.S. biomedical research groups. A variety of unusual or unique opportunities exist in foreign countries for pursuing studies of substantial importance to medical science in general and to the health of U. S. residents in particular. Investigations in the field of geographic pathology and epidemiology on an international basis are likely to provide important clues to the causes of certain diseases which cannot be studied adequately in more restricted environments.

Program Plans in 1968 and 1969

The period of training is for two years, and approximately five new IRCDP associates are appointed each year. Each assignment is tailored specifically to the background and interest of the associate, as well as the projected needs of the Public Health Service. In 1969 no new associates will be appointed so that a phasing out of this type of overseas assignment will be accomplished. The five positions will then be available for appointment of fellows to study under international agreements such as the US-Japan and US-Italy Cooperative Medical Science Agreements. The intent here is to provide manpower resources which will add to the attacks on diseases of mankind without adding to dollar payments outside the U.S. The new associates will be international in the sense that they will take training in and work on biomedical problems which international agreements have spotlighted for joint effort.

Division of Computer Research and Technology

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | 101 | $1,129,000 | 108 | $1,236,000 | +7 | +$107,000 |
| Other expenses..... | | 3,426,000 | | 3,548,000 | | +122,000 |
| Total..... | 101 | 4,555,000 | 108 | 4,784,000 | +7 | +229,000 |

Introduction

The Division of Computer Research and Technology conducts a continuing program in computation as a necessary general research support to the NIH Institutes and Divisions. The planning, conduct and management of the high quality research programs at NIH generates a wide variety of tasks in applied mathematics, computer operations and computer programming and in the design and creation of special purpose, computer-based data handling systems.

Program Plans in 1968 and 1969

In 1967, recognizing the increasing demands for advanced computation, NIH began to install modern computing equipment. This change is now essentially complete; new equipment has been installed and the reprogramming tasks are about at an end. During the past calendar year, the performance of the new equipment has improved significantly; unit cost of computing is at least one-third less and in some applications has been reduced to one-half. The throughput (jobs completed per unit time) capability of the system has increased 7 to 10 times that of a year ago.

This progress has been brought about by improved reliability and stability in the computing equipment and the development of better computer operating systems by the Division staff in cooperation with the equipment manufacturer. For the remainder of 1968 and during 1969, the effort will be focused on developing the necessary responsiveness of the central equipment to permit linking, via remote terminals, selected laboratories and clinics to the central facility.

Concomitant with equipment development has been a highly successful effort to recruit an adequate number of key personnel in the areas of applied programming. With the improved equipment and new staff, DCRT has initiated several collaborative biomedical studies with investigators in the several Institutes and Divisions. Excellent progress has been made in the general area of analyzing physical biochemistry data: mass spectrometric and

spectrophotometric data on important biological molecules are analyzed routinely on the computer in support of studies on chemical structure and biological activity. DCRT's expanding program includes two major activities in these important physical chemistry studies: first, the design and implementation of small, laboratory systems to provide expanded, rapid, accurate acquisition and editing of data for the same unit cost; and secondly, the undertaking of difficult theoretical studies on chemical structure which can lead to better understanding of the pharmacological actions of these compounds.

Collaborative studies with the cardiac surgeons in the National Heart Institute have led to the creation of mathematical routines suitable for the rapid analysis of certain hemodynamic functions important to reconstructive cardiac surgery. This effort will be continued including the development of a direct data link between the central computer facility and the surgical suites to provide timely analysis at greatly reduced cost.

A number of tasks in support of clinical research and delivery of clinical care are now underway. Administrative functions in support of patient care are being processed by the computer. In depth studies to identify the information elements essential to clinical study and care of patients are being conducted in an effort to identify an economical solution to the information handling problems of hospitals. Increasing costs of equipment has forced DCRT to seek a solution using the central computer facility supported by telephone line links. This important, complex problem will be of continuing concern for some time to come.

Continuing financial and personnel support has been given to the automation of the clinical laboratories in the Clinical Center. These scientists have made considerable progress: a number of the several hundred procedures have been automated. Continued support in 1969 is planned. Much of this development effort should be transferable, directly or with subsequent modification, to the care of patients in other hospitals.

A collaborative project with the Neurology Institute involving computer analysis of the normal and pathological anatomy of neural tissue is underway. This effort, known generally as image processing, is representative of collaborative efforts that will be undertaken with several other Institutes and Divisions. Progress has been made in specifying the needed computing equipment and a number of analytical routines for handling the photographic images has been formulated and tested using the central facility equipment as well as off-site computing equipment. The key mathematical staff to support this large, difficult task has been recruited. A project with the National Cancer Institute involving computer processing of the natural English diagnostic statements of pathology is proceeding well. Testing for routine use of this computer-based system will begin late in 1968. The long-range goal of this project is the expansion of these mathematical and logical algorithms to process clinical discharge summaries and ultimately, clinical records. This will enable the clinician to process both the non-numeric

data essential to laboratory and clinical research and the delivery of clinical care and services.

The Division is requesting an additional seven (7) positions and $229,000 for 1969. The new positions and $66,000 will be used throughout the Division's major programs to complement the present staff resources required to sustain efforts initiated in 1968 and in prior years and to develop an effective time-shared computer system as the next step in more efficient use of the central facility. Adequate staff is needed to continue progress toward the development of software for responsive man-machine communication systems. Another need is for continued developmental efforts in the central facility to make the general-purpose computer more accessible to the user. Finally, and most important, staff will be required to design a time-shared computer system for the support of medical management functions required in the operation of the NIH Clinical Center. The technology required to develop an operational time-shared system for hospitals is still lacking and efforts must be intensified to make progress in this area. Part of the problem rests not with the computer technology but with the difficulty in arriving at specific definitions of existing hospital functions and in the rapid changes which are taking place in these functions.

The remaining program increase of $120,000 will be used to meet the normal growth in the demand for the computer services and to provide for automated support of clinical laboratories, including the development of more efficient means of monitoring critically ill patients. Included in the requested net increase is $31,000 for the annualization of positions new in 1968 and $10,000 for the annualization in 1969 of the 1968 pay raise cost. There is also an increase of $2,000 for centrally furnished services from the "National Institutes of Health Management Fund".

Engineering Development

Obligations by Activity

| | 1968 Estimate | | 1969 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Direct operations: | | | | | | |
| Collaborative research and development..... | -- | -- | -- | $1,000,000 | -- | $1,000,000 |
| Program direction..... | 5 | $344,000 | 5 | 347,000 | -- | +3,000 |
| Total obligations..... | 5 | 344,000 | 5 | 1,347,000 | -- | +1,003,000 |
| Unobligated balance, reserve..... | 1 | 3,000 | -- | -- | -1 | -3,000 |
| Total obligations and reserves..... | 6 | 347,000 | 5 | 1,347,000 | -1 | +1,000,000 |

The efforts of this activity are directed towards applying engineering and technological innovations to biomedical problems. The budget request proposes an increase of one million dollars to permit a wider range of program activities including the funding of a number of collaborative research and development projects. At the suggestion of the Congress, the NIH will go forward with the development of a new organizational structure which will consolidate the operations necessary to manage the technical and research programs of the fields of biomedical engineering--a new and complex discipline created by pioneering teams of exceptional engineers and biomedical scientists--and medical engineering development. This new central organization, budgeted for 5 positions in 1968 and 1969, will provide coordination for existing biomedical engineering activities of the NIH. It will include participation from the individual Institutes and Divisions so as to insure an appropriate NIH-wide integration of effort and thereby provide a more centralized focus for both the leadership and the engineering and scientific competences necessary for supporting a wide range of collaborative research and development projects at NIH.

Essential to a program of targeted research is the ability to map out a route to a desired objective, identifying the paths to be followed and the sequence of steps to be taken in its attainment. In the furtherance of this approach, NIH has engaged the National Academy of Engineering--in an advisory capacity--to assist program management in delineating the organizational, functional and operational relationships that may be needed and how such relationships may be utilized to create the most effective interplay of the many disciplines required for the effective application of engineering and technical innovations to program problems.

The amount requested will make it possible to augment the engineering and scientific staffs in the new unit and to utilize the contractual mechanisms for targeted research projects which, heretofore, have not moved forward due to the lack of resources needed to obtain the necessary competences for a number of highly integrated developmental projects relating to programs of research. In order to move ahead in a very complex area, it is necessary to develop imaginative new coupling devices and to establish a central point where a broad range of talents may interact and engage in a collaborative exchange of ideas, methodologies and techniques. The increase will provide additional support to a key area of special program effort and bring to bear the specific applications of modern engineering technology in bio-medicine and health in such areas as:

a. Instrumentation,
b. Artificial internal organ replacement,
c. Automation and its integration into the hospital environment,
d. Isolation and containment facilities,
e. Patient monitoring devices and systems,
f. Hospital information systems.

If additional support is available for bioengineering and medical engineering development, it will significantly hasten the transmission of new knowledge, developed in the applied areas of these programs, to the vatious components of the nation's health care system.

$1,000,000 of the total increase will provide for the initiation of contracts and $3,000 for centrally furnished services from the "National Institutes of Health management fund."

INTERNATIONAL CENTER

| | 1968 estimate | | 1969 estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|
| | Pos. | Amount | Pos. | Amount | Pos. | Amount |
| Personnel compensation and benefits..... | -- | -- | 10 | $64,000 | +10 | +$64,000 |
| Other expenses..... | -- | -- | -- | 536,000 | -- | 536,000 |
| Total..... | -- | -- | 10 | 600,000 | +10 | +600,000 |

Introduction

The proposal for the establishment of an International Center relating to the biomedical and behavioral sciences at the National Institutes of Health has a number of antecedents. The earliest formal expression of such a possibility culminated in the International Health Research Act of 1960 (P.L. 86-610).

It was the continuing hope of the late Representative John E. Fogarty of Rhode Island, through many years of his career, to create, at NIH, a Center dedicated to international cooperation and collaboration in health, medical and biological research. This idea was presented by Congressman Fogarty before the Third National Conference of World Health in September 1963.

Following Congressman Fogarty's death last January, Representative Melvin Laird, of Wisconsin, proposed to the Congress the establishment of an International Study and Conference Center at NIH as a memorial to John E. Fogarty. In February 1967, the President, in his message to the Congress on Education and Health in America, stated that he was seeking the funds to establish an International Center for Advanced Study in the Health Sciences at NIH. In consequence, $500,000 was included in the 1968 HEW appropriation bill for planning funds to construct the "John E. Fogarty International Center for Advanced Study in the Health Sciences" at the National Institutes of Health as a suitable memorial to the interest and contribution of Congressman John E. Fogarty to the medical sciences generally and the programs of NIH particularly. This new organizational element is being established to develop and operate a number of essential NIH functions with general international character.

The John E. Fogarty International Center represents the continuing effort of the NIH to promote maximum effectiveness of the NIH research establishment at Bethesda by mobilizing and developing research potential wherever it may be, toward the advancement of research in the life sciences.

Since the search for new knowledge knows no national boundaries, the ability of NIH, through the programs of the International Center, to initiate research into health problems of international scope is only a natural extension of NIH's long term objectives.

The initial function of the Fogarty Center will be to create the environment, and provide the means, to assemble scholars, scientists and innovative minds for advanced study of the development of science as it relates to health and its implications and applications for the future.

Until such time as construction of a new International Center facility is completed Stone House (Building 16) will be restored to serve as a base for the initiation of the Center. Apart from the long term utility of this building to the program, its early availability will make it possible to institute a significant part of the Center's program during the fiscal years 1969 and 1970.

Plans for the new Center construction include conference facilities, living quarters for scholars in residence, guest-type rooms for visiting conference participants, food service facilities, lounges, and office space for the Center staff.

Program Plans

In addition to being a Center for Advanced Study and the locus for the conduct of an organized program of international conferences and seminars concerned with the life sciences, the Center will undertake other programs aimed at extending international cooperation in the advancement of the health sciences:

I. Scholars in Residence Program

The International Center will be equipped with flexible facilities on the NIH reservation which would be suited to the assembly of outstanding scientists and scholars from the U.S. and abroad, invited to the Center for varying lengths of time. The central location and planned programs would serve to promote the continuing interaction of the scholars with each other and their hosts, and would minimize outside distractions. The facilities would include space for scholars of international distinction to pursue individual or small group projects which have a bearing on the health of society. Removed for a time from the immediacy of daily problems, they could give thought to long-range issues, including assessments on the state of the art and philosophical and social concepts relative to the thrust of science and its applications. In this connection a continuing series of studies would be made on such matters as the further direction of fundamental biomedical science, the implication of the advance of science and technology for the future of medical education and medical services, the issues surrounding increasing capability for biological manipulation. In addition, distinguished scientists will be invited to interact more closely with intramural NIH research activities.

II. International Conference and Seminar Program

The development of a well-organized international conference and seminar program centered in the contemporary status of the life sciences, as well as the facilities to house such a program will be a primary aim of the Center. Under this program the Fogarty Center will organize and sponsor a series of working conferences on current directions in medical, biological and behavioral sciences, and their relationship to health and the advance of well being. The objective is to purposely bring together international experts and to offer the appropriate forum for creative discussion of a wide range of matters of importance to the advancement of the sciences relevant to health and their relationship to society. Selection of appropriate subjects and assignment of priority will be decided by the Director and staff of the Fogarty Center with the assistance of an Advisory Committee. During the forthcoming year conference programs on the subjects of "The Science Base for Medical Education in the Future," "The Study of Disease in Controlled Populations," and the scientific, legal, and ethical issues of organ transplantation are contemplated.

Follow-up action based on the conclusions of these conferences and seminars will be sought through NIH Institutes and, should international action be necessary, through collaborative arrangements with other countries or by one of the international agencies with health science programs.

III. International Fellowship and Exchange Program

A. Senior Scientist Exchange Program

Provision will be made for a series of awards on an international basis to encourage the exchange of senior teachers and scientists among universities and research institutions in foreign countries and the U.S. This program would make it possible to place distinguished scientists in posts throughout many countries and in the U. S. for a period of one to five years in order that the broadest scientific influence can be exerted by such outstanding individuals.

B. International Postdoctoral Fellowship Program

This program provides a series of awards on an international basis to support the study and training of promising foreign postdoctorate students in the health sciences in the U.S. The Postdoctoral Fellowships Program has been in existence at NIH for over 10 years and will be transferred to the Fogarty Center from the Office of International Research.

IV. Foreign Visitor Reception

The influx of visitors and delegations from foreign countries has become a pressing problem for NIH and has created a crucial need for a reception center. The Fogarty Center will serve as the focal point for

reception and guidance of scholars in residence, visiting scientists and guests. A well developed reception program would allow us to gain the maximum benefit from foreign scientists visiting the NIH, while at the same time acquainting them with U. S. scientific and cultural facilities.

Budget Request

In order to initiate, on a modest scale, the new programs outlined above and to assemble the necessary staff to operate them, $600,000 and 10 new positions are requested.

THURSDAY, MARCH 21, 1968.

# GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES

## WITNESSES

DR. THOMAS J. KENNEDY, JR., DIRECTOR, DIVISION OF RESEARCH FACILITIES AND RESOURCES
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
KENT SMITH, ASSISTANT EXECUTIVE OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES
DAVID TILSON, CHIEF, HEALTH RESEARCH FACILITIES BRANCH, DIVISION OF RESEARCH FACILITIES AND RESOURCES
BERTIL G. BERGQUIST, BUDGET OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

| | 1967 actual | 1968 estimate | 1969 estimate |
|---|---|---|---|
| Program by activities: | | | |
| Grants: | | | |
| 1. Health research facilities | 35,001 | 37,793 | 20,608 |
| 2. Centers for research on mental retardation | 5,419 | 607 | |
| Total program costs, funded—obligations (object class 41.0) | 40,420 | 38,400 | 20,608 |
| Financing: | | | |
| Unobligated balance available, start of year | −27 | −15,608 | −12,208 |
| Unobligated balance available, end of year | 15,608 | 12,208 | |
| New obligational authority (appropriation) | 56,000 | 35,000 | 8,400 |
| Relation of obligations to expenditures: | | | |
| Total obligations (affecting expenditures) | 40,420 | 38,400 | 20,608 |
| Obligated balance, start of year | 148,390 | 150,037 | 149,437 |
| Obligated balance, end of year | −150,037 | −149,437 | −131,045 |
| Expenditures | 38,773 | 39,000 | 39,000 |
| Expenditures are distributed as follows: | | | |
| Out of current authorizations | 3,877 | 4,000 | 4,000 |
| Out of prior authorizations | 34,896 | 35,000 | 35,000 |

Mr. FLOOD. Now we will hear about "Grants for construction of health research facilities."

We have Dr. Thomas J. Kennedy, Jr., Director of the Division of Research Facilities and Resources.

### BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

We will put Dr. Kennedy's biographical sketch in the record. (The biographical sketch follows:)

Name: Thomas J. Kennedy, Jr.
Position: Director, Division of Research Facilities and Resources.
Birthplace and date: Washington, D.C., June 24, 1920.
Education: Catholic University of America, Washington, D.C., B.S., 1940; Johns Hopkins University, Baltimore, Md., M.D., 1943.
Experience: Director, Division of Research Facilities and Resources, NIH, 1965 to present; Special Assistant to the Director for Scientific Communications, Office of the Director, NIH, 1962–65; assistant to the Director of Laboratories and Clinics, Office of the Director, NIH, 1960–62; attending physician

and responsible clinical investigator, National Heart Institute, NIH, 1953–60; Investigator, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, NIH, 1950–60; associate (research) in medicine, George Washington University School of Medicine, Washington, D.C., 1951–65; S.A. Surgeon—Medical Director, USPHS, 1950 to present; research fellow, Research Service, First (Columbia) Medical Division, Goldwater Memorial Hospital, New York City, 1949–50; assistant in medicine, Columbia University College of Physicians and Surgeons, New York City, 1948–50; resident physician, Research Service, First (Columbia) Medical Division, Goldwater Memorial Hospital, New York City, 1947–49; research fellow, NYU College of Medicine, New York City, 1945–47; research fellow, Research Service, Third (NYU) Medical Division, Goldwater Memorial Hospital, New York City, 1945–47; first lieutenant and captain, AUS, assigned to Office of Scientific Research and Development, 1944–47; intern, Medical Service, Peter Bent Brigham Hospital, Boston, Mass., 1944.

Association memberships: American Federation for Clinical Research; American Physiological Society, American Board of Internal Medicine.

Mr. FLOOD. You may proceed, Dr. Kennedy.

## GENERAL STATEMENT

Dr. KENNEDY. Mr. Chairman and members of the committee, I am here to speak on behalf of the President's request that $8.4 million be appropriated for the health research facilities program for 1969.

### PROGRAM HISTORY

This program was created in the summer of 1956 by the passage of the Hill-Bridges Health Research Facilities Act, whose authority has been renewed four times. The objectives of the original authorization, which were reaffirmed each time the program was renewed, were to expand throughout the Nation physical facilities for the conduct of research in the sciences related to health by constructing new facilities, by renovating or remodeling substandard facilities, and by replacing obsolete facilities which could not be renovated economically. These objectives continue to be valid.

The availability of resources to expand health research facilities throughout the United States coincided in time with the enlargement of our national commitment to support biomedical research and training. Enormous growth in research in the sciences related to health and tremendous advances in knowledge have occurred during this period, which could not have taken place without this program. The exciting work in cardiovascular surgery, pioneered by distinguished investigators such as Drs. DeBakey, Kantrowitz, and Shumway have been done in facilities partly funded by grants from the health research facilities program. Drs. Kornberg and Goulian did their recently reported epochmaking work on the synthesis of DNA—popularly described as the creation of living matter in the test tube—in facilities built with the assistance of health research facilities program funds. These are but two examples of many which could be enumerated. The full array of clinical and basic science investigation on all of the serious diseases with which medical research is concerned is conducted in space provided in part by this program. Many outstanding medical scientists have received their graduate research training in such facilities.

### PROJECT SUPPORTED

Since the inception of the program $445 million has been awarded as the Federal portion of 1,144 construction projects, encompassing

over 18 million net square feet of well-equipped research space. Grants-in-aid have been tendered to 405 institutions in every State of the Union as well as Puerto Rico and the District of Columbia. The total construction cost of these projects is well over $1 billion.

The need to add space to accommodate high quality scientific activity continues strong. All of the leading research institutions are crowded, many very seriously.

NEEDS FOR ADDITIONAL RESEARCH SPACE

Growth in population, with the attendant increase in societal needs of all sorts, has generated pressures to expand existing academic institutions and to create new ones. One major bottleneck limiting the rate of enlargement of these institutions has been the small manpower pool from which faculty members must be drawn. In the specific context of this presentation, additional health research facilities are key to the development of the research-oriented scholars to staff new and expanding schools engaged in biomedical research, and also to provide the environment to attract such scientists, once trained, to permanent academic careers. Thus the flow of service-oriented health care specialists is closely coupled to the availability of adequate health research space.

Specific new national commitments present inescapable requirements for research space. For example, the creation by the National Heart Institute of the Cardiovascular Research and Training Centers which the Congress has approved will increase the need for construction of space to house the activity. Public Law 89-544, which regulates the transportation, sale, and handling of certain laboratory animals, has given rise to an increasing demand for renovation, replacement, and, in many cases, expansion of laboratory animal facilities. There has been a noticeable increase in applications to the health research facilities program for such facilities in response to the passage of this legislation.

SUMMARY OF BUDGET

In summary, Mr. Chairman, Federal funds for the construction of health research facilities continue to constitute an essential component of the overall Federal commitment to health research. For the continued viability of this program, I lend my wholehearted support to the President's request of $8.4 million for 1969. This amount, when added to the $12.2 million held in reserve from funds appropriated in fiscal year 1968, will provide a total of about $20.6 million for obligation during 1969.

I shall be happy to respond to any questions.

Mr. FLOOD. You plan to obligate $38,400,000 and leave unobligated $12,208,000 of the total funds available. This $12,208,000 will carry forward to 1969? When you add that to the requested appropriation of $8,400,000, that will make $20,608,000 available for obligation.

Dr. KENNEDY. That is correct.

Mr. FLOOD. So, even with the carryover, you are budgeting a reduction of $17,792,000 for 1969; is that right?

Dr. KENNEDY. That is correct, sir.

Mr. FLOOD. How was this request for $8,400,000 arrived at? Do you have a plan or a goal? Do you have a target?

Dr. KENNEDY. I think this figures was essentially given to us, sir.

Mr. FLOOD. Given to you? Who gave it to you?

Dr. SHANNON. Mr. Flood, this was given to Dr. Kennedy by my office.

Mr. FLOOD. Let me put it this way: What did you ask for?

Dr. KENNEDY. The Division requested the residual authorization. Fiscal year 1969 is the third year of a 3-year authorization. We asked for $195 million.

Mr. FLOOD. What?

Dr. KENNEDY. $195 million.

Mr. FLOOD. Your budget was reduced a little, wasn't it?

COMPARISON BETWEEN PROGRAM DEMAND AND BUDGET

How big is the gap between your legitimate demand, which we recognize, and what you are budgeting for this year and next year?

Dr. KENNEDY. We expect, Mr. Flood, to have about $95 million in Council-approved applications on our books by the close of this fiscal year, and we expect to—in terms of our negotiations with academic institutions and other things, our preliminary discussions, what we know is likely to come in, in the following year—we expect about another $100 million to be approved in fiscal year 1969. So, for the available funds, there will probably be claims of about $200 million.

Mr. FLOOD. How do you establish priorities for whatever funds you do have? How do you do that?

Dr. KENNEDY. The priorities are essentialy established by the priority ratings accorded these by the scientific review bodies who assess the merits of the programs proposed for these new facilities.

Dr. SHANNON. There is another thing Dr. Kennedy might mention and that is that there are certain things that have inherently high priorities. Where research facilities, under the present law, are part of the construction of a totally new medical school, they would have a very high priority, or where a research facility is essential in order to implement the program of an agreed-upon institute—such as the dental research centers that we talked about in connection with the dental appropriation. That, too, would give it a very high priority. Or if the inability to meet the rigid application of animal-care standards would put an important research installation out of business, this, too, would give it a very high priority. We do have some very broad guidelines that deal with classes of construction grants rather than with individual construction grants.

It should be obvious to the committee, Mr. Chairman, that with the sums available to Dr. Kennedy, as contrasted with his realistic estimate of the need, no projects, other than those that are in the category of superexcellence or extraordinarily urgent need, will be satisfied with this budget.

Now, as a matter of principle, Dr. Kennedy does not operate by taking whatever funds he has and attempting to spread them over many, many projects, but rather to assess the minimal need to accomplish a specific purpose and then to make enough funds available to make the project go. So relatively few construction grants will be made within these general guidelines.

Mr. FLOOD. Are there questions?

Thank you very much.

JUSTIFICATION MATERIAL

Public Health Service

Grants for Construction of Health Research Facilities

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $35,000,000 | $8,400,000 |
| Unobligated balance brought forward | 15,607,934 | 12,207,934 |
| Unobligated balance end of year | -12,207,934 | --- |
| Total | 38,400,000 | 20,607,934 |

Obligations by Activity

| Page Ref. | | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|---|
| 172 | Grants for construction and equipment: | | | |
| | (a) Health research facilities | $37,792,775 | $20,607,934 | -$17,184,841 |
| | (b) Centers for research on mental retardation | 607,225 | --- | -607,225 |
| | Total obligations | 38,400,000 | 20,607,934 | -17,792,066 |
| | Unobligated balance reserve | 12,207,934 | --- | -12,207,934 |
| | Total, obligations and reserve | 50,607,934 | 20,607,934 | -30,000,000 |

Obligations by Object

| | | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|---|
| 41 | Grants, subsidies, and contributions (total obligations) | $38,400,000 | $20,607,934 | -$17,792,066 |

## Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $35,000,000 |
| Unobligated balance brought forward | 15,607,934 |
| Unobligated balance end of year | -12,207,934 |
| 1968 total estimated obligations | 38,400,000 |
| 1969 estimated obligations | 20,607,934 |
| Total change | -17,792,066 |

Decreases

Program

| | |
|---|---|
| Health research facilities | -17,184,841 |
| Centers for research on mental retardation | -607,225 |
| Total decreases | -17,792,066 |
| Total net change requested | -17,792,066 |

## Explanation of Changes

The net decrease of $17,792,066 is the result of a decrease of $26,600,000 in appropriated funds (the difference between $35,000,000 appropriated for 1968 and $8,400,000 requested for 1969) adjusted by unobligated balances at the beginning and end of 1968 and 1969 as follows: $15,607,934 brought forward from 1967 making the gross amount available for obligation $50,607,934 in 1968, of which $12,207,934 will be carried forward to 1969; the $12,207,934 unobligated balance brought forward from 1968 plus $8,400,000 the amount requested for 1969 will provide a total of $20,607,934.

Authorizing Legislation

| Legislation | 1969 Authorization |
|---|---|
| Public Health Service Act<br>Section 701(b)--It is therefore the purpose of this part to assist in the construction of facilities for the conduct of research in the sciences related to health by providing grants-in-aid on a matching basis to public and nonprofit institutions for such purpose..... | $195,000,000 1/ |

PUBLIC HEALTH SERVICE ACT

Title VII--Health Research and Teaching Facilities and Training of Professional Health Personnel

Part A--Grants for Construction of Health Research Facilities

Appropriation

Section 704. There is hereby authorized to be appropriated for the fiscal year ending June 30, 1957, and for each of the nine succeeding fiscal years, not to exceed $50,000,000, and for the fiscal year ending June 30, 1967, and the two succeeding fiscal years, an aggregate of not to exceed $280,000,000, for making grants-in-aid for the construction of facilities for research, or research and related purposes, in the sciences related to health; and any sums appropriated pursuant to this section shall remain available until expended.

1/ This amount is the balance of the 1967-1969 fiscal years authorization of $280,000,000 less the $50,000,000 and $35,000,000 appropriated in fiscal years 1967 and 1968 respectively.

Grants for Construction of Health Research Facilities

| | 1968 Estimate Amount | 1969 Estimate Amount | Increase or Decrease Amount |
|---|---|---|---|
| Health research facilities | | | |
| Appropriated | $35,000,000 | $8,400,000 | -$26,600,000 |
| Unobligated balance brought forward | 15,000,709 | 12,207,934 | -2,792,775 |
| Subtotal | 50,000,709 | 20,607,934 | -29,392,775 |
| Unobligated balance end of year | -12,207,934 | --- | 12,207,934 |
| Subtotal, HRF | 37,792,775 | 20,607,934 | -17,184,841 |
| Centers for research on mental retardation | | | |
| Unobligated balance brought forward | 607,225 | --- | -607,225 |
| Total | 38,400,000 | 20,607,934 | -17,792,066 |

The primary objectives of the Health Research Facilities program are to meet needs for new and replacement facilities for the Nation's research in the health sciences. In addition, the program assists in the construction of biomedical research facilities in new and expanding medical schools and the construction and renovation of research animal facilities. Modern facilities are essential to the Nation's colleges, universities, and research institutions in effectively prosecuting research efforts leading to better health for the American people. This program provides assistance to non-profit institutions by means of grants for up to 50 percent of the necessary costs of the facility, and requires that such facilities be used by the recipient for research in the health sciences for a minimum of ten years.

Medical schools committed to expanding their enrollments for the purpose of providing the Nation an increased number of physicians have been aided by the Health Research Facilities program in providing research space required by expanding faculty. New medical schools have been assisted in their endeavors to develop a basic complement of research facilities for core faculty.

The Health Research Facilities program has also been an important element in initiating programs related to high priority national biomedical research objectives in fields such as aging, dental health, human reproduction, and pharmacology-toxicology.

To support research in preclinical biomedical scientific disciplines such as cystology, biochemistry, molecular biology, and genetics, and in clinical sciences, such as oncology, cardiology, surgery, opthalmology, pediatrics, and psychiatry, research-service type facilities such as animal facilities, instrumentation laboratories, clinical research units, etc. are required.

Although the Health Research Facilities program has been able to meet some of the foregoing needs, the imbalance between the rate of research manpower development and the rate of facilities construction, replacement, and renovation is steadily widening. This trend will continue and result in serious overcrowding of research space. Against this increasing imbalance between the demand for the supply of research facilities, the $20,608,000 requested will provide approximately 589,000 net square feet of research space (based on $70.00 per net square foot) and provide space for an aggregate faculty expansion of approximately 589.

Historically, total appropriations of $465,000,000 have been made by the Congress through 1968 for Health Research Facilities construction. Since the inception of the program, 1,930 applications have been received requesting a total of $809,440,328.

Upon recommendation of the National Advisory Council on Health Research Facilities, the Surgeon General has thus far awarded 1,448 grants, totalling $445,252,574. This amount for construction is more than doubled by the nonfederal matching funds contributed by the grantees.

| | |
|---|---|
| Medical Schools | $244,867,897 |
| Dental Schools | 9,328,760 |
| Schools of Public Health | 9,749,889 |
| *Other health-related schools | 92,387,101 |
| **Institutions other than health-related schools | 88,918,927 |
| Total | 445,252,574 |

*Includes schools of veterinary medicine, pharmacy, osteopathy, nursing, chemistry and biological sciences.
**State, County and Municipal Health Agencies as well as hospitals and independent research institutions.

Grants made under this program include support for the construction of large multipurpose facilities as well as providing for relatively small additions to existing facilities. Specific examples of projects awarded during the past year are the following:

Private Nonprofit Medical Schools

| | |
|---|---|
| University of Chicago<br>Chicago, Ill. | $903,000 |
| New addition to the medical school for cancer research | |
| Hahnemann Medical College and Hospital<br>Philadelphia, Pa. | 6,903,000 |
| Construction of research space in a new medical college building for the basic and clinical sciences | |
| Mount Sinai School of Medicine<br>New York, N. Y. | 7,945,000 |
| New medical school with HRF space for research in basic medical sciences. Also some remodeling in the Atran and Berg buildings | |
| Duke University<br>Durham, N. C. | 1,218,000 |
| Central laboratory animal facilities | |

Public Medical Schools

| | |
|---|---|
| University of Arizona<br>Tucson, Ariz. | 500,000 |
| Construction of research space in a proposed clinical sciences building which is an expansion of the medical school | |
| Ohio State University<br>Columbus, Ohio | 723,000 |
| Construction of phase I of a laboratory animal center consisting of four one-story buildings | |
| University of Texas Southwestern Medical School<br>Dallas, Texas | 1,894,000 |
| Construction of basic science research laboratories in a new basic sciences building to house the departments of anatomy, physiology, pharmacology and biochemistry | |

Private Nonprofit

Children's Hospital Medical Center
Boston, Mass. $2,091,000

Laboratory facilities in a new basic pediatrics sciences building

University Hospitals of Cleveland
Cleveland, Ohio 952,000

Construction of research facilities for the department of pediatrics in the new Rainbow Babies and Children's Hospital

The $8,400,000 requested for 1969 plus the unobligated balance of $12,208,000 carried forward from fiscal year 1968 would be used to help meet some of the following estimated requirements:

| | |
|---|---|
| Balance of recommended grants as of June 30, 1968.... | $102,000,000 |
| Applications approved by F.Y. 1969 councils..... | 90,000,000 |
| Total estimated requirements..... | 192,000,000 |

THURSDAY, MARCH 21, 1968.

# GENERAL RESEARCH SUPPORT GRANTS

## WITNESSES

DR. THOMAS J. KENNEDY, JR., DIRECTOR, DIVISION OF RESEARCH FACILITIES AND RESOURCES
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
KENT SMITH, ASSISTANT EXECUTIVE OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES
BERTIL G. BERGQUIST, BUDGET OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES
LELAND B. MAY, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
CHARLES MILLER, CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We will now take up general research support grants.

## GENERAL STATEMENT

Dr. KENNEDY. I welcome this opportunity to appear before you in support of the general research support program and its budget for 1969. This program is financed through funds transferred from the appropriations of the several Institutes into an account administered by the Division of Research Facilities and Resources. For this reason, the general research support allocation does not appear as a formal proposal for funds to be appropriated in the President's budget; rather, it is set forth as a line item in the budget submissions of the various categorical Institutes.

### LEGISLATIVE HISTORY AND PROGRAM OBJECTIVES

The general research support program, created under the authority of Public Law 86–798, was explicitly designed to strengthen the biomedical research programs of institutions significantly engaged in this activity. The avowed objectives of this program were to enable them to cultivate scientific excellence by building institutional strength; to enlarge their role in determining the direction of their research and research training programs, and to balance these programs in accordance with their own long-range research aspirations; to explore emerging opportunities in research through the pursuit of new and/or unorthodox ideas; to foster early recognition and support of scientific talent; and to attract an increasing amount of non-Federal research funds for their institution.

At the present time, the program is composed of three distinct elements known respectively as the general research support, the biomedical sciences support, and the health sciences advancement award programs.

GENERAL RESEARCH AND BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAMS

The general research support grant program has since 1962 provided flexible support, in an amount proportional to an institution's identifiable direct biomedical research expenditures, to health professional schools, to biomedical research institutes, to research-oriented hospitals, and to State and local health departments. The biomedical sciences support grant program is similar in most respects, but eligibility for it is limited to nonhealth professional components of graduate schools.

These two programs deliberately permit and encourage institutions to exercise broad discretionary control in the use of the grant funds, provided that the expenditures are for research and research training in the health sciences. In addition, the programs furnish institutions with an unparalleled opportunity to administer grant funds creatively within the context of their own long-range research objectives. The flexibility with which these funds can be used means that they are particularly suited to the task of coupling institutional goals with the missions of the various Federal agencies; at the same time, this pliancy allows them to redress imbalances created by the zeal with which Federal agencies have pursued their statutory missions.

During 1967, 387 institutions were tendered support through these programs. Of these, 271 were academic and 116 were nonacademic organizations such as research-oriented hospitals and research institutes. Of the 271 academic institutions receiving aid of this nature, there were 178 schools for training health professionals—in medicine, dentistry, public health, veterinary medicine, pharmacy, and osteopathy—and 93 nonhealth professional components of graduate schools.

Each year, progress reports from the grantee institutions cite numerous research accomplishments derived from the use of these funds and thereby verify the immense benefits accruing to the Nation's health. For example:

> The Albert Einstein Medical Center in Philadelphia is convinced that skillful deployment of small general research support awards has been the major factor in the expansion of its research program from virtually zero in 1960 to a current annual level of $2.5 million.
>
> At the University of Colorado, a screening tests devised for evaluating the intellectual and behavioral development of children from birth to 5 years, has proven so valuable that the American Academy of Pediatrics has recommended its routine use of pediatricians, and it has been adopted on a nationwide basis for evaluating Project Headstart children.

There can be no question that these two grant programs have served as a powerful instrument to help institutions throughout the Nation strengthen and expand their health-related research capabilities.

HEALTH SCIENCE ADVANCEMENT AWARD PROGRAM

Biomedical research is an activity almost totally dependent upon the academically based scientific research community. As a result of the growing governmental investment in biomedical research, the

Congress has shown an increasing interest in developing a broader base of scientifically excellent academic institutions. It has become more and more evident that a few outstanding medical centers cannot constitute a research community large enough to serve the entire Nation.

In 1966, the NIH announced a competitive program to encourage comprehensive institutional advancement toward excellence in biomedical research and research training. Called the health sciences advancement award program, it provides grants to carefully selected colleges and universities that can become institutions truly distinguished in research and research training by developing their facilities, staff, and research potential. Five new awards were initiated in 1967 in addition to the two begun in 1966. With these new awards, the centers will emerge to help in the conquest of disease.

### SUMMARY OF BUDGET

The President's budget requests $60.7 million for 1969, $1.0 million above the operating level for 1968, for this complex of programs, as follows: $48.2 million for the traditional general research support programs; $7.5 million for the biomedical sciences support grant program; and $5 million for support of the health science advancement award program. This request is not in addition to but is already included within the research grants budgets of the several Institutes and divisions of the NIH and the National Institute of Mental Health, from which the funds are transferred and aggregated for general research support programs.

I shall be happy to answer any questions.

Mr. FLOOD. Actually it is not an appropriation; it is just authority to transfer from certain appropriations, is that right?

Dr. KENNEDY. It is just an accounting to you, sir, of how this money is being used.

Mr. FLOOD. You are asking for authority to transfer $60,700,000 in 1969 compared with authority you have in 1968 to transfer $61,700,000.

Dr. KENNEDY. That is correct.

Mr. FLOOD. But you do not plan to use $2 million of the 1968 authority.

You compare the request with the authority you have now— and you are asking for a reduction of $1 million.

Dr. KENNEDY. That is correct.

Mr. FLOOD. Compare the request with the authority you plan to use in 1968. That is an increase of $1 million.

Dr. KENNEDY. That is correct.

### HEALTH SCIENCES ADVANCEMENT AWARDS

Mr. FLOOD. You have an increase for what you call health sciences advancement awards.

There has been some controversy about this program. What is your assessment, currently, of its value?

Dr. KENNEDY. We can talk with some authority about what has happened in the two institutions which received awards in 1966. This past October, progress on these two awards was reviewed and there is

every reason to think that the funds made available through this program have had a significant and catalytic effect in transforming these institutions very remarkably. I must qualify my specific attribution of success to this award because a number of other factors operated in both institutions. So that the health science advancement award to the Medical School at the University of Virginia and to the Division of Biological Sciences at Cornell, in Ithica, were part of a multipronged offensive on the development of those schools. But in a sense, both the NIH and other agencies such as the Ford Foundation in the case of Cornell, simultaneously recognized that these institutions were candidates for a great leap forward and funds from several sources have in a sense complemented each other and potentiated the effect of each other. The overall effect has been quite dramatic.

METHOD OF CALCULATING INSTITUTE CONTRIBUTIONS

Mr. FLOOD. In your justification on the last page you show that most of the institutes will contribute a little less to this fund in 1969 than 1968. A few of them are up.

How do you calculate the amounts to be transferred?

Dr. KENNEDY. They represent a uniform percentage of the research grant budgets of each institute.

Dr. SHANNON. Mr. Flood, could I explain the mechanics of this: This is viewed as a discrete activity and the sum needed to achieve its specific objective is determined. Each of the Institutes then contributes, from its appropriation for research grants, a constant percentage to make up the sum total.

In other words, one has to make the primary decision: Shall one go forward with the Health Science Advancement Award and if so, at what level—all things being considered. Having determined that, then the computation is made and a part of that sum is then charged to each of the appropriations. So it is sort of a "backed into" figure.

NEW HEALTH SCIENCE ADVANCEMENT AWARDS

Mr. SHRIVER. These Health Sciences Advancement Awards, you say five new awards were initiated in 1967. Who were the recipients of those?

Dr. KENNEDY. The recipients were the University of Oregon, the University of Colorado, Purdue University, Vanderbilt University, and Washington University in St. Louis.

Mr. SHRIVER. Include in the record for how much.

Dr. KENNEDY. I can say on the average they were about a half million dollars a year each.

(The information requested follows:)

*Health Sciences Advancement Awards—1967 New Awards*

| *Institution* | *Amount awarded* |
|---|---|
| University of Colorado | $687,000 |
| University of Oregon | 695,000 |
| Purdue University | 564,000 |
| Vanderbilt University | 620,000 |
| Washington University | 592,000 |

SCHOOLS OF VETERINARY MEDICINE

Mr. SHRIVER. I wouldn't expect you to put in all of these 387 institutions, but let's just pick out one of these. The veterinary medicine part of it. There are 18 or 19 schools. Not all of those would have received grants for research. Which ones did?

Dr. KENNEDY. Thirteen of the 18 schools of veterinary medicine received it. There is an eligibility threshold that must be crossed in order to qualify for the program. That is to say, an institution must reach a certain critical size, and at that point is deemed in need of general research support, to redress some of the imbalances, and so forth.

(The names of the schools follow:)

SCHOOLS OF VETERINARY MEDICINE WHICH RECEIVED GENERAL RESEARCH SUPPORT AWARDS IN 1967

University of California at Davis.
Colorado State University.
University of Illinois.
Purdue University.
Iowa State University.
Michigan State University.
University of Minnesota.
University of Missouri.
New York State Veterinary College at Cornell University.
Ohio State University.
Oklahoma State University
University of Pennsylvania.
Washington State University.

Mr. SHRIVER. Thank you. That is all I have.

Mr. FLOOD. This completes our hearings with NIH. As usual you have done an excellent job, Dr. Shannon, as have the various Institute Directors. And, as I said at the beginning of these hearings, I hope you are back with us in the same capacity next year.

Dr. SHANNON. Thank you very much.

92-892 O-68-pt. 5—63

JUSTIFICATION MATERIAL

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

General Research Support Grants

Amounts Available for Obligation

| | 1968 | 1969 |
|---|---|---|
| Appropriation | $61,700,000 | $60,700,000 |
| Unobligated balance end of year | -2,000,000 | --- |
| Total | 59,700,000 | 60,700,000 |

Obligations by Activity

| Page Ref. | | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|---|
| | Grants: | | | |
| 184 | (a) General research support | $48,200,000 | $48,200,000 | --- |
| 184 | (b) Biomedical sciences support | 7,500,000 | 7,500,000 | --- |
| 185 | (c) Health sciences advancement awards | 4,000,000 | 5,000,000 | +$1,000,000 |
| | Total obligations | 59,700,000 | 60,700,000 | +1,000,000 |
| | Unobligated balance reserve | 2,000,000 | --- | -2,000,000 |
| | Total, obligations and reserve | 61,700,000 | 60,700,000 | -1,000,000 |

Obligations by Object

| | 1968 Estimate | 1969 Estimate | Increase or Decrease |
|---|---|---|---|
| 41 Grants, subsidies, and contributions (total obligations) | $59,700,000 | $60,700,000 | +$1,000,000 |

Summary of Changes

| | |
|---|---|
| 1968 enacted appropriation | $61,700,000 |
| Unobligated balance end of year | -2,000,000 |
| 1968 total estimated obligations | 59,700,000 |
| 1969 estimated obligations | 60,700,000 |
| Total change | +1,000,000 |

Increase

Program:

| | |
|---|---|
| Health sciences advancement awards | 1,000,000 |

Explanation of Change

The program increase of $1,000,000 will provide support for two additional new health sciences advancement awards.

Authorizing Legislation

| Legislation | 1969 Authorization |
| --- | --- |
| Public Health Service Act<br>Section 301(d)--Make....grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs..... | Indefinite |

PUBLIC HEALTH SERVICE ACT

Title III--General Powers and Duties of Public Health Service

Part A--Research and Investigation

Appropriation

Section 301(d). Make....grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs: Provided, that such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research or research training projects for any fiscal year through the appropriations for the National Institutes of Health may be transferred from such appropriations to a separate account to be available for such research and research training program grant-in-aid for such fiscal year.

General Research Support Grants

Introduction

Strong and effective institutions are indispensable to the betterment of health care and to the improvement of fundamental conditions of human life. Academic and research institutions produce the scientific manpower, ideas, and techniques that are essential to the growth of concepts that relate to health, disease and to the application of medical knowledge.

The General Research Support grant program contributes to the development of research capabilities of institutions by (1) providing flexible general support to health professional schools, hospitals, and non-academic non-profit institutions; (2) extending similar general support to other academic institutions which are heavily engaged in health-related research and research training; and (3) providing support designed to accelerate the advancement of existing capabilities in health research and related graduate research training activities within institutions which have demonstrated an appropriate base for the achievement of scientific excellence.

Program Plans

Traditional General Research Support Program: This program will continue to provide encouragement to health professional and other health-related institutions to meet emerging opportunities in research, to explore new and unorthodox scientific ideas, and to use research funds in ways that will contribute to long range development of institutional capability in health research and in the environment for research. It makes possible the recruitment of faculty and other professional personnel, the retention of senior investigators, and the support of research associates and research trainees in a variety of disciplines. In addition, general research support funds are used to initiate, support and expand research facilities, exclusive of construction costs, needed by many investigators within an institution. Other uses of general research support funds include the creation of new research and research training opportunities, the support of exploratory research projects by young investigators and the acquisition of costly apparatus necessary for the proper conduct of research activities. Under this program approximately 311 separate awards are now made to schools of medicine, dentistry, osteopathy, pharmacy, public health and veterinary medicine, and to hospitals, research institutes, research foundations, and state and municipal health departments.

Biomedical Sciences Support Grant Program: This program extends the concept of general research support to academic institutions other than the health professional schools. The National Institutes of Health has long recognized the importance to the Nation of the contributions to the health sciences made by investigators and teachers in academic components not covered by the traditional General Research Support program, as demonstrated by the fact that a significant proportion of research project grants, graduate training grants, center grants, etc., go to these components.

It is essential that flexible general research support funds be provided in order that the project-oriented funds may be utilized most effectively in these institutions, and that they may have benefits similar to those that now accrue to the health professional and health-related schools. Approximately 96 institutions are funded under this program in 1968.

Health Sciences Advancement Award Program: In 1966 funds were provided to advance the health sciences, primarily in graduate academic institutions. The Health Sciences Advancement Award Program supports institutions which are not yet pre-eminent in the health sciences, but which offer a strong base of biomedical research and research training. This support which is catalytic in nature will enable the institutions to attain a new level of achievement and to continue their advancement beyond the period of the grant. Approximately nine health sciences advancement awards will be made in 1968. In contrast to the formula basis of the two preceding programs, these awards are made on the basis of selection on merit in national competition, and are of limited duration.

Distribution of Funds by Program Area in 1969

The requested amount of $60,700,000 would be distributed as follows: $48,200,000 for the General Research Support to approximately 326 institutions; $7,500,000 for Biomedical Sciences Support Grants to approximately 99 institutions; and $5,000,000 for Health Sciences Advancement Awards to approximately 11 institutions.

The following table illustrates the planned 1968 and 1969 distribution of general research support grants:

| | 1968 Estimate | | 1969 Estimate | |
|---|---|---|---|---|
| | No. | Amount | No. | Amount |
| General Research Support | | | | |
| Educational Institutions: | | | | |
| Dentistry | 49 | $2,892,000 | 49 | $2,800,000 |
| Medical | 95 | 26,125,000 | 99 | 26,450,000 |
| Osteopathy | 5 | 193,000 | 5 | 180,000 |
| Public Health | 12 | 2,072,000 | 13 | 2,000,000 |
| Pharmacy | 10 | 578,000 | 11 | 550,000 |
| Veterinary Medicine | 15 | 1,928,000 | 16 | 1,900,000 |
| Noneducational Institutions: | | | | |
| Hospitals | 72 | 7,905,000 | 77 | 7,840,000 |
| Research Foundations, Institutes and Others | 51 | 6,025,000 | 54 | 6,030,000 |
| Health Departments | 2 | 482,000 | 2 | 450,000 |
| Subtotal | 311 | 48,200,000 | 326 | 48,200,000 |
| Biomedical Sciences Support Grants | 96 | 7,500,000 | 99 | 7,500,000 |
| Health Sciences Advancement Awards | 9 | 4,000,000 | 11 | 5,000,000 |
| Total | 416 | 59,700,000 | 436 | 60,700,000 |

The general research support grants program is administered by the staff and funds of the Division of Research Facilities and Resources. Grant funds are provided by applying a uniform percentage to the amounts provided for research grants in the appropriations of the several institutes and one division of the National Institutes of Health, and the National Institute of Mental Health.

The following table shows the estimated amounts to be provided by each contributing appropriation:

| | 1968 Estimate | 1969 Estimate |
|---|---|---|
| National Institutes of Health | | |
| National Cancer Institute | $6,899,000 | $6,838,000 |
| National Heart Institute | 9,809,000 | 9,425,000 |
| National Institute of Dental Research | 1,256,000 | 1,194,000 |
| National Institute of Arthritis and Metabolic Diseases | 9,551,000 | 9,409,000 |
| National Institute of Neurological Diseases and Blindness | 8,094,000 | 7,430,000 |
| National Institute of Allergy and Infectious Diseases | 5,169,000 | 5,289,000 |
| National Institute of General Medical Sciences | 7,989,000 | 8,127,000 |
| National Institute of Child Health and Human Development | 4,264,000 | 4,082,000 |
| Division of Environmental Health Sciences | 547,000 | 551,000 |
| General Research and Services:- Office of International Research | 639,000 | 600,000 |
| Subtotal, NIH | 54,217,000 | 52,945,000 |
| National Institute of Mental Health | 5,483,000 | 7,755,000 |
| Total | 59,700,000 | 60,700,000 |

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