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DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1968

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HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETIETH CONGRESS

FIRST 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
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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
NATIONAL INSTITUTE OF MENTAL HEALTH

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THURSDAY, APRIL 6, 1967.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NATIONAL INSTITUTES OF HEALTH
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G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We have with us now Dr. James A. Shannon, Director of the National Institutes of Health.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

We have a biographical sketch, "Curriculum Vitae," of Dr. Shannon, which we will place in the record at this point. Everybody knows about him around here and respect his excellent record.

(The sketch follows:)

Name: James Augustine Shannon.
Date & 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:
- 1929–1931: Intern, Bellevue Hospital, New York City.
- 1931–1932: Clinical Assistant Visiting Physician, Third (N.Y.U.) Medical Division, Bellevue Hospital, New York City.
- 1931–1932: Assistant in Physiology, New York University College of Medicine, New York City.
- 1932–1935: Instructor in Physiology, New York University College of Medicine, New York City.
- 1935–1941: Assistant Professor of Physiology, New York University College of Medicine, New York City.
- 1936: Guest Investigator, Physiological Laboratory, Cambridge University, England.

1938–1942: Assistant Visiting Physician, Third (N.Y.U.) Medical Division, Bellevue Hospital, New York City.
1941–1942: Assistant Professor of Medicine, New York University College of Medicine, New York City.
1941–1946: Director, Research Service, Third (N.Y.U.) Medical Division, Goldwater Memorial Hospital, New York City.
1942–1946: 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.
1944–1945: Acting Director, Third (N.Y.U.) Medical Division, Goldwater Memorial Hospital, New York City.
1946–1947: Chairman, Malaria Study Section, National Institutes of Health, Bethesda, Maryland.
1946–1949:
Director, Squibb Institute for Medical Research, New Brunswick, New Jersey.
Special Consultant to Surgeon General, U.S. Public Health Service.
Member, Study Section, National Institutes of Health, Bethesda, Maryland.
1949–1952: Associate Director (In Charge of Research), National Heart Institute, National Institutes of Health, Bethesda, Maryland. (Appointed to Commissioned Corps, Public Health Service, 1949.)
1952–1955: Associate Director (In Charge of Intramural Affairs), National Institutes of Health, Bethesda, Maryland.
1955–: Director, National Institutes of Health, Bethesda, Maryland.

Activities during the War:

1941–1946:
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 1959–1962; Fellow 1956.
American Society for Pharmacology and Experimental Therapeutics.
American Society for Clinical Investigation.
Society for Experimental Biology and Medicine.
American Association for Advancement of Science.
Association of American Physicians.
Washington Academy of Sciences.
Harvey Society.
Alpha Omega Alpha.
Sigma Xi.

Professional Activities:

1951–1956: Member, Subcommittee on Malaria of the Committee on Medicine, National Research Council.
1952–1956: Member, Subcommittee on Shock of the Committee on Surgery, National Research Council.
1953–1956: Chairman, Malaria Panel, National Research Council.
1953–1954: Member, Panel on Allocation of Gamma Globulin, National Research Council.
1953–: Member, Division of Medicine Sciences, National Research Council.
1953–1960: Member, Executive Committee, Division of Medical Sciences, National Research Council.

1955–: Public Health Service Representative, Division of Medical Sciences, National Research Council.
1955–1962: Member, United States National Committee for the International Union of Physiological Sciences.
1954: Member, Board of Directors, Gorgas Memorial Institute of Tropical and Preventive Medicine.
1956–1966: Member, Expert Advisory Panel on Malaria, World Health Organization.
1959–1963: Member, Advisory Committee on Medical Research, World Health Organization.
1962–1966: Member, Advisory Committee on Medical Research, Pan American Health Organization.
1959–1965: Consultant, President's Science Advisory Committee.
1963–: Consultant to Advisory Committee on Research to the Agency for International Development.
1965:
Department of Health, Education, and Welfare Alternate Representative to Federal Council for Science and Technology.
U.S. Delegate to the United States-Japan Cooperative Medical Science Committee.

Honorary Degrees:

1952: Doctor of Science, College of the Holy Cross.
1957: Doctor of Laws, Notre Dame.
1958:
Doctor of Science, Duke University.
Doctor of Science, Providence College.
1959: Doctor of Science, Loyola University, Chicago.
1960:
Doctor of Science, Catholic University.
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.
Doctor of Medicine, Karolinska Institute, Stockholm, Sweden.
1965:
Doctor of Science, University of Maryland.
Doctor of Science, New York University.
Doctor of Science, The Jefferson Medical College and Medical Center, Philadelphia.

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, Vilanova University.
1962: Public Welfare Medal, National Academy of Sciences.
1964: Rockefeller Public Service Award.
1965:
Election to Membership in the National Academy of Sciences.
Honorary Fellowship in American Association of Hospital Administrators.
1966:
Public Health Service Distinguished Service Medal.
The Modern Medicine Award for Distinguished Achievement in Medicine.
Presidential Distinguished Federal Civilian Service Award.
Honorary Member, American Hospital Association.
John M. Russell Award, Markle Foundation.

Abraham Flexner Award, Association of American Medical Colleges.
Alan Gregg Lecturer.

General Statement

Mr. Flood. I see you have a prepared statement. Generally you submit your statement for the record, as I recall it, and speak extemporaneously, do you not?

Dr. Shannon. I would like to do that again, sir.

Mr. Flood. At this point in the record we will insert the doctor's prepared statement, and then he will talk extemporaneously.

(The statement follows:)

Statement by Director, National Institutes of Health, Public Health Service

Mr. Chairman and members of the committee, there are twelve separate appropriations in the Bill now before you which, together, provide funds for the programs of the National Institutes of Health. The Directors of the appropriate Institutes and Divisions will provide detail about the specific aims, accomplishments, and needs of the activities supported by each of these appropriations. This statement speaks to their common purposes and their common problems.

Medical research in this country has been, and is, so closely interwoven with the evolution of the NIH support programs that it will be logical—and, I think, of special interest to the new members of this Committee—to outline the development of these programs.

At present, about 40 percent of our total national expenditure for medical research is provided through the NIH appropriations. NIH is by far the largest single source of support for medical research in this country. The character of the programs through which this support is provided—and, incidentally, the manner in which they are administered—plays a substantial role in determining the character and directions of our national medical research effort and, in a very real sense, the quality of life of the American people. I suspect that most Americans agree with the view expressed some years ago by Professor Will Durant, who popularized philosophy in the 1930's, that "The health of nations is more important than the wealth of nations."

The tremendous strides that have been made during the past twenty years in our understanding of biological processes and in our ability to deal effectively with many disease problems has added immeasurably to our national wealth. This is true if this progress is estimated, however imprecisely, in economic terms—such as added years of individual productivity or the reduction in time lost from work. It is overwhelmingly true if the measure is humanitarian—the suffering that has been eased or prevented, the lessening of permanent disability, the young children and young parents whose lives have been saved, or the increasing number of people who are able to enjoy a vigorous and healthy old age. It is difficult to estimate in a meaningful way the consequences to a child and his family of the avoidance of death or disability due to polio, or the restoration to normal development of the child with complex congenital heart disease, much less the consequences to the family unit of the early detection and care of uterine cancer.

There is in progress a quiet revolution in the practice of medicine as the result of research. The advent of antibiotics has sharply reduced the ravages of unpreventable infections; new techniques for cardiac and other forms of surgery have made it possible to intervene in situations which a decade or two ago were beyond surgical help; drugs for the control of hypertension have significantly reduced the death rate for heart disease among middle-aged persons; a number of viral vaccines are now in common use.

The American Medical Association recently reported that the introduction of new products has been so dynamic that 7 out of 10 now on the market were not available ten years ago.

New knowledge has greatly changed the approach to the treatment of disease and the attitude of the practicing physician to science. Fifty years ago, few physicians were concerned with scientific investigations—their main professional interest was the application of existing empirical knowledge which changed very

little from year to year. Today, while relatively few practicing physicians are themselves engaged in formal research, they are fully aware of the impact of science on their capability to diagnose and treat disease.

But I am less concerned about the progress of the past than I am about the vast problems that still remain to be solved.

Despite the great strides forward in recent years, the biomedical sciences are still in a primitive stage of development. The lack of understanding of underlying causes is still the main barrier to the solution of the major chronic illnesses. Much of biological research must continue to be descriptive and observational and its approach to the solution of problems is still, necessarily, empirical. The unifying and clarifying principles and "laws" that transformed alchemy into chemistry and natural philosophy into physics have yet to be uncovered in the life sciences. In fact, too frequently a major step forward brings into view still larger—and more forbidding—areas of unknown territory. For example, the success in combating bacterial infectious diseases laid bare, for all to see, the puzzling roles that seem to be played by viruses in both acute and chronic diseases.

The puzzling and exasperating delays that mark the progress of medical research are due to the large gaps in fundamental knowledge. The history of immunization against infectious diseases provides a typical example. The demonstration that inoculation with infective material from a calf would prevent smallpox took place in 1796 but because it came about without any real understanding of the nature of the disease or of the principle of vaccination, it remained, for nearly a century, simply a technique for preventing a specific disease. Not until Pasteur, Koch and others established the principles of bacteriology in the 1880's, was it possible, in a relatively short time, to control such diseases as diphtheria, tetanus, bubonic plague, and scarlet fever.

Even so, basic knowledge was still insufficient to cope with many other infectious diseases. The existence of "ultravisible viruses" was deduced in 1898 but many years elapsed before it became possible to isolate them or grow them in a laboratory. Polio, for example, was identified as a virus disease as early as 1909 but it took more than 40 years of scientific effort on many related problems to pave the way for a successful vaccine. Not until the 1950's were knowledge of the disease and techniques for vaccine development adequate to the task. It is, incidentally, instructive to note that the tissue culture techniques used were the result of research having no direct relation to the polio problem. They were developed partly by scientists studying the characteristics of cancer cells and partly by scientists trying to improve the production technology of the fermentation industry.

We are now in a period of rapid development of viral vaccines that is, in many ways, comparable to the progress that followed Pasteur's discoveries 80 years ago. In addition to the polio vaccines, we now have vaccines for such common viral diseases as yellow fever, influenza and measles and for several less common respiratory diseases. In the foreseeable future, we shall have vaccine for German measles (rubella), mumps, and a number of other respiratory diseases whose causative viruses have been identified.

In other fields, the problems are more difficult. For the chronic diseases with which medical research is now primarily concerned—heart disease, cancer, an array of metabolic and neurological diseases, and congenital defects—the valleys of ignorance are broader than the peaks of knowledge. The exploration of the cause of these diseases or defects—which must precede the development of wholly effective treatment and preventive measures—is most formidable. In fact, many of these diseases probably have no single cause. Rather, the cause of disease and the determinants of the rate of progress in dealing with it are likely to be a combination of chemical and biological, environmental and developmental, and behavioral and sociological factors. A total understanding of these diseases will require research in many disciplines and in many directions.

The change in the pattern of major health problems from the acute infectious to the more complex chronic diseases and the consequent change in the research emphasis is paralleled in the evolution of NIH and its programs.

NIH had its beginnings in 1891 in a small bacteriological laboratory at the Marine Hospital on Staten Island. This was soon transferred to Washington and became the Hygienic Laboratory. For its first 20 years, it was exclusively concerned with communicable diseases which were then the major public health problem and accounted for more than half of all deaths. About the time of World War I, its activities were gradually expanded. The Hygienic Laboratory dis-

covered the cause of pellagra, a dietary deficiency disease then common in the South, it did pioneering work in the study of shock resulting from immunizations, and it formulated the first sound theory about personal sensitivity that helped to lay the foundation for the study of allergies—which were until then unknown and unsuspected.

As the application of the new science of bacteriology progressively brought the major infectious diseases under control, the death rate for these diseases rapidly declined—from 648 per 100,000 population in 1900 to 208 in 1937. By 1950 the rate was down to 65—a tenth of what it had been half a century before. But partly as a result of this success, the other major causes of death and the so-called chronic diseases loomed larger as national health problems. The death rate for malignant neoplasms rose from 64 in 1900 to 112 in 1937, for cardiovascular and renal diseases from 345 to 455, and many people who would formerly have fallen victim to diphtheria, smallpox or typhoid fever now survived to enjoy an arthritic old age. The first significant step to extend the research activities of NIH to these fresh areas of public concern was the creation of the National Cancer Institute in 1937.

The National Cancer Act of 1937 marks a sharp turning point in the history of NIH. It set the stage for a series of actions which were completely to alter the scope, orientation and mechanisms not only of the NIH programs but of the whole national biomedical research effort. The ultimate effect of the pattern set by the Act was—

> To focus attention on specific diseases, or groups of diseases, and to authorize special programs to discover the cause, facilitate the diagnosis, improve the treatment, and, hopefully, devise preventive measures for these diseases;
>
> To complement the research conducted by NIH itself with grants-in-aid to non-Federal institutions for research projects directed towards the same ends;
>
> To give NIH responsibility not only for the conduct and support of biomedical research but for research-training through the award of fellowships; and
>
> To dramatize these disease-oriented programs—and give them greater public visibility—by grouping them in separate categorical Institutes named for the major disease entities within their area of responsibility.

The transformation did not, of course, come about all at once. The Cancer Act merely authorized a comprehensive cancer program that included research projects grants and fellowships for this purpose only. Its immediate effect was to create twin Institutes in 1937—the National Institute of Health and the National Cancer Institute—on the new grounds in Bethesda. But the new grant program awarded only 9 research project grants, totaling $91,000, in 1938.

The intervention of World War II slowed the pace of development and—except for budget increases to off-set war-time inflation and to pay for special war-related research projects undertaken by NIH—the situation remained fairly static. In 1945, the two Institutes had appropriations totaling $2.8 million of which $170,000 was for research grants. Total national expenditure on medical research, from all sources, at this time was about $70 million.

The Public Health Service Act of 1944 extended the authority to award research-project and research-training grants to the other programs of NIH and prepared the way for the post-war transfer to NIH of the medical research projects sponsored by the war-time Office of Scientific Research and Development.

The creation of the other categorical Institutes then followed in rapid order. In 1948, the National Heart Institute and the National Institute of Dental Research were created by acts of Congress which, at the same time, created NIH's present 'federal' structure and changed its collective name to the National Institutes of Health. A National Microbiological Institute was administratively established—its name subsequently changed to the National Institute of Allergy and Infectious Diseases as its scope enlarged. In 1949, the Division of Mental Hygiene became the National Institute of Mental Health. In 1950, the Congress created the National Institute of Neurological Diseases and Blindness and the National Institute of Arthritis and Metabolic Diseases.

This organizational growth was accompanied by considerable construction at the Bethesda campus, which was largely completed by 1953, and appropriate increases in the direct operating budget. There was, however, little program expansion during the period from 1950 to 1956. While this was partly due to the Korean war, it was also, necessarily, a period during which the new Institutes

clarified their goals and program policies, the grant mechanisms were refined, and a stable administrative apparatus was developed.

The grant mechanisms were well established and the direct operation was well underway by fiscal year 1956. The eight appropriations for the National Institutes of Health for that year totaled $98.5 million of which $40.5 million was for research grants and contracts, $17.3 million for training grants and fellowships, $28.3 million for direct research, $10.4 million for public health and disease control activities, and $2 million for administration and program management.

The next step in the evolution of the NIH programs was the passage of the Health Research Facilities Act of 1956. This legislation, which authorized matching grants for the construction of research facilities, rounded-out the scope of NIH activities so that they then had available the essential mechanisms for the development of a meaningful research program national in scope. NIH could finance the training of scientists, it could enhance the physical plant available for scientific endeavors, and it could provide for the assistance needed in the actual conduct of research.

The period of rapid program expansion was initiated after Mr. Folsom, who was then Secretary of HEW and deeply concerned about the consequences of serious illness, undertook a thorough inquiry into the quality of the NIH operations, the opportunities that existed for productive research, and the level of funding that would be required to take advantage of these opportunities. He came to the conclusion that the expansion of productive research should be limited only by the number of highly qualified scientists available. He proposed substantial increases in the NIH budget both for research and for training. The Congress immediately responded to his assessments of the problem. Broad program needs were immediately satisfied and from 1957 through 1963 the appropriations were increased, largely as the result of specific actions by the Congress, at a rate of approximately 30 percent per year.

For 1965—which ended a decade of very rapid, across-the-board growth—the cost of this new complex enterprise was at the level of $1.0 billion.

Program development since 1964 has not been as general or undifferentiated as it was during the period of rapid growth. Rather, this has been a period of selective development. The NIH has continued to support activities which, by scientific consensus, are considered to be important and relevant to serious disease problems. However, increasing staff time has been devoted to an analysis of the ongoing activities and deficient areas have been identified for special examination. Frequently it was found that these areas, though important, were not progressing because they did not conveniently fit into the usual discipline orientation of the academic enterprise. It became increasingly obvious that special organizational arrangements would be required if such fields were to flourish and to make their contributions to the complex of problems under study.

Some of these program-problem areas are of sufficient importance to list as examples of this programing activity:

Special problems that relate to the causation of cancer and the intimate interplay of chemicals and viruses;

Problems of aging, many of which involve complex and inter-acting biological, psychological, environmental and social factors;

Research in pharmacology and toxicology which is concerned not only with drug development and the identification and prevention of adverse reactions but also with the problems created by the increasing chemical hostility of the manmade environment in which we live;

Development of the dental sciences to establish a sounder scientific base for the advancement of modern dentistry;

Problems of child development which, as in the case of aging, involve a complex array of factors and which can result in life-long disabilities and vulnerabilities to disease; and, finally,

Greater emphasis on special problems, such as deafness, and disease that can result in blindness.

The definition of some of these broad problem areas led, very early, to the establishment of two non-categorical Institutes which became operational in 1963. The National Institute of Child Health and Human Development was established because the categorical, disease-oriented approach of the other Institutes is not well-suited to the exploration of problems that involve the complex problem of human development. A more comprehensive research approach is needed to shed light on this cycle of experience that is common to every human being. The creation of the National Institute of General Medical Sciences recognized

that the categorical programs of the major Institutes depend on many common areas of science no one of which could properly be assigned to an individual Institute. The vigor of these common areas is an important determinant of progress in each and every Institute. The new Institute was assigned responsibility for the health and vigor of these common scientific undertakings.

A new dimension was added to NIH by the Heart Disease, Cancer and Stroke Amendments of 1965. The assignment to NIH of responsibility for the Regional Medical Programs constitutes a major commitment to a program that, though research-related, is primarily service-oriented.

This program grew out of the recommendations of the President's Commission on Heart Disease, Cancer and Stroke. Simply stated, its purpose is to extend the excellence of medicine in the academic setting to the primary battle ground of disease where it occurs, that is, in a community setting.

The present programs of the National Institutes of Health now comprise five major groups of activities:

(1) The conduct of research in its own laboratory and clinical facilities, and through contracts with other institutions;

(2) The support of research through grants;

(3) The support of training of highly-qualified scientists and clinicians for research careers;

(4) The construction of health research facilities through matching grants; and

(5) The support of a national program to strengthen medical service through the new Regional Medical Programs.

I should like to indicate briefly how the $1,187,250,000 requested for FY 1968 is distributed among these five major activities.

Funds for direct operations include $81.7 million for the conduct of research by the NIH scientific staff and $113 million for goal-oriented collaborative projects; $644.5 million is for the support of research through grants; $194.6 million is for the training grants and fellowship programs; $35 million is requested for the Health Research Facilities Construction program; $59.4 million is for the new Regional Medical Program; $59 million is for other direct operations, program direction, administrative services and management of the extramural program.

The bulk of the NIH budget is devoted to the support of medical research, and closely related activities, outside its own laboratories and clinics. However, funds requested for research conducted by NIH itself, are substantial. The extraordinary excellence of these scientific activities set the level of excellence of the whole enterprise. The competence and personal involvement of NIH scientists with the major research problems on the frontiers of the biosciences provides a solid and indispensable intellectual base for all other NIH activities.

The Committee will wish to consider what role the NIH programs should play in the future and to decide—in the light of the testimony for the various Institutes—what activities are desirable and feasible. I am confident that the amounts requested in the budget estimates will be amply justified by the benefits that will accrue to the people of this country from the activities that these funds will support.

Dr. SHANNON. Mr. Chairman, the statement that I have submitted embraces the general development of medical research in the Nation and its relationship to the parallel development of the National Institutes of Health, and ends by outlining the activities that will be funded by the budget request which is before you.

I thought it would probably be appropriate, with a number of new members on the committee, to address myself to the generalities of the program and put before you certain comparative measurements of research and development, the Federal role in research and development in the biomedical sciences, and particularly the role NIH plays in this and certain derivative considerations from these facts.

Mr. FLOOD. What is biomedicine? This record should show the meaning of some of these medical terms.

Dr. SHANNON. Biomedicine is a vernacular term, which has come into use during the past 10 or 15 years, that encompasses all the fields

of research that are relevant to the ultimate solution of the problems of medicine. These fields, necessarily, include many biological disciplines that are not directly concerned with specific considerations of the disease itself.

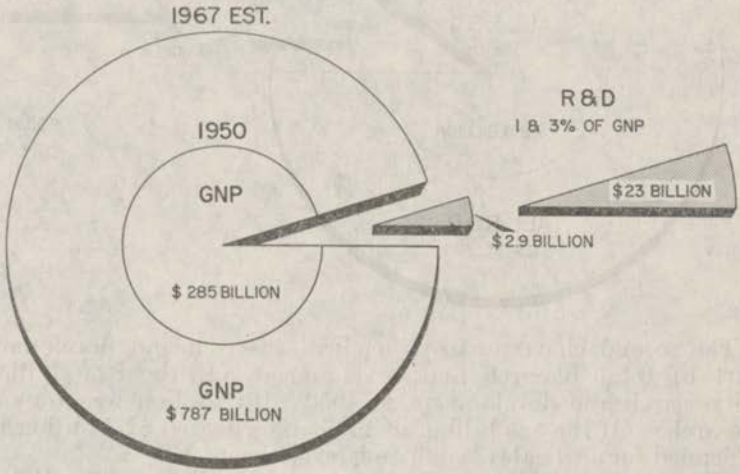
It is a rather all-embracing term that includes behavioral, biological, and clinical research in one package. I think the term "biomedical research" probably is more descriptive of the total NIH activity than any other single term.

Mr. Chairman, I have a series of relatively simple charts which will reproduce very well in black and white. We were able, through Mr. Fogarty's courtesy, 2 years ago, to insert similar charts in the record, because they highlight certain salient features of the operation and make the text much more understandable.

Mr. FLOOD. Without objection, we will insert the charts at the appropriate places in the record as you progress with your testimony.

(The first chart follows:)

ALL RESEARCH AND DEVELOPMENT AS A PROPORTION OF GROSS NATIONAL PRODUCT 1950-1967



NATIONAL EFFORT IN RESEARCH AND DEVELOPMENT

Dr. SHANNON. The first chart, Mr. Flood, outlines the increase in all research and development, from all sources, in the period 1950–67.

Mr. FLOOD. Represents what?

Dr. SHANNON. All research and development, regardless of source, in the entire Nation in 1950 as contrasted to 1967.

In 1950, the gross national product was $285 billion. Research and development amounted to $2.9 billion. In 1967, the estimated gross national product is $787 billion and it is estimated that $23 billion will be spent on research and development, again from all sources.

Mr. FLOOD. How is that ratio standing up?

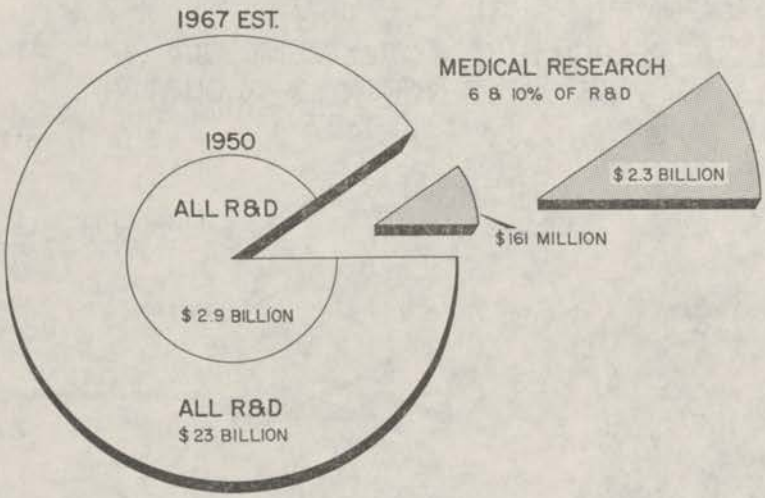
Dr. SHANNON. It changes from 1 percent in 1950 to an estimated 3 percent in 1967, with the largest part of that change taking place subsequent to 1957.

Mr. FLOOD. Of course, that 3 percent has built up over a series of years.

Dr. SHANNON. During the past 15 years, more particularly during the past decade.

MEDICAL RESEARCH AND DEVELOPMENT

MEDICAL RESEARCH AS A PROPORTION OF ALL RESEARCH AND DEVELOPMENT 1950-1967



The second chart portrays medical research and development as part of total research and development. Of the $2.9 billion for all research and development in 1950, $161 million was for medical research. Of the $23 billion in 1967 an estimated $2.3 billion will be expended for medical research and development.

That represents a change from 6 percent of all research and development being in the medical sciences in 1950——

Mr. FLOOD. How long have you been running this shop?

Dr. SHANNON. Twelve years, sir.

This represents an increase from 6 to 10 percent.

Mr. FLOOD. Actually, the great percentage of this has come about during your tenure.

Dr. SHANNON. Yes, sir.

This chart is very important because the growth of research has too frequently been described as uncontrolled and unrestrained. The activity has been accused of having money to burn or overstuffed programs or money that cannot be used effectively. I would call to your

attention the base in 1950, which was $161 million. If you divide that between 9 Institutes, such as we have today, it would be less than $20 million per Institute. If it were divided between the 80 medical schools and 40 dental schools, it would amount to $1.3 million per institution. It would support the work of less than 5,000 full-time scientists. On the basis of 50 States, it would amount to the expenditure of $3.2 million on medical research per State.

In 1950, the medical schools, hospitals, and research institutions had recovered from World War II. They had reassembled their staffs. Broad use had been made of the GI bill of rights which had produced a very large reservoir of trained scientists for whom there was no support.

Mr. FLOOD. This indicates that military service does not necessarily destroy an interest in proceeding with learning after service.

Dr. SHANNON. I would agree, sir, that the motivation to learn subsequent to service is substantial. During the war I had a substantial number of young officers assigned to me, and more than 80 percent of them are now full professors spread across the Nation.

Mr. FLOOD. In my class in college for my bachelor's degree in 1924, right after World War I, there were so many veterans that the nickname of the class was "The Soldats and the Gobs."

Dr. SHANNON. Mr. Chairman, I graduated from college in 1925, and we, too, had a substantial number of people who were in college subsequent to service in World War I.

The increase in medical research from 6 to 10 percent of all research and development is, in part, a reflection of the simple expansion of all technology and of all of our national ventures as we move into a new type of technically oriented society. But, in part, it remedies a gross deficiency, and reflects an appreciation of the very broad capabilities of medicine and medical research to provide new knowledge of direct relevance to the ills and ailments of our people. It represents a determination to launch a very broad attack on major areas of disease and disability that show marked opportunity for advancement.

RESEARCH PROJECTS TERMINATED BY NIH

Mr. FLOOD. Did you ever abandon a research project?

Dr. SHANNON. Yes, sir. I left medical school in 1929 and had experience in a hospital in 1929 through 1931. I joined the staff of the department of physiology for the subsequent 9 years. I was heavily involved in radiophysiology which was then in process of developing most of the modern techniques that are now used in that field of research.

I left it and joined the department of medicine and undertook——

Mr. FLOOD. I mean at NIH.

Dr. SHANNON. Oh, yes, sir.

Mr. FLOOD. Suppose you provide at this point in the record a list of research projects that started out glowingly, but that you eventually abandoned.

Dr. SHANNON. I can mention one that started off very glowingly but which washed out, although this is unusual. In the early days of my appearance before this committee, it appeared that glutamine, which is a derivative of amino acid, was likely to be the answer for

a very serious form of convulsive disorder, epilepsy. It turned out in the course of the subsequent 2 or 3 years that it indeed did, together with asparagine, release a small number of people from their epileptic seizures.

Mr. FLOOD. Would you list some of those?

Dr. SHANNON. We will be glad to give you some examples because our program does have internal dynamism.

Mr. FLOOD. You understand the problem?

Dr. SHANNON. Yes. We will furnish that information.

(The requested information follows:)

DISCONTINUED PROJECTS AND PROGRAMS OF THE NIH

Biomedical research is conducted in the Direct Operations of the National Institutes of Health and supported by its Extramural Grants. The basic component in both areas are the Research Projects of individual scientists or groups of scientists. These projects may be grouped together and considered as Programs where this is scientifically sound and administratively desirable. In general, a program falls within the province of a single Institute or Division of the National Institutes of Health and derives from the mission of the Institute or Division. Projects, therefore, are discontinued or reoriented with much greater frequency than programs. Programs organized for specific, fixed tasks are disbanded when the job is finished or proves unfeasible. However, if its scientific area is complex and rapidly developing and its scientists are creative and adaptable, a program may change over the years by a series of small steps as each part progresses. As long as the change is gradual and productive there need be no compulsion to relabel an enterprise or to stop it formally and start it again under a more precisely descriptive title. This kind of unadvertised progression is not limited to NIH programs. Perhaps the most striking example of diversity under an unchanging title has occurred at the Carnegie Institution of Washington, where the extremely productive Department of Terrestrial Magnetism has housed, among other things, work on biochemistry, molecular biology and computer simulation of learning.

An apt and adequate description of the terminations and changes in the substance of NIH programs over the years must, therefore, provide a sense of the numbers of individual projects which have been discontinued and at the same time should include some specific examples of the many programmatic changes which have occurred in response both to sweeping advances in biomedical science and to specific opportunities offering unusual promise.

PROJECTS TERMINATED

The Institutes and Divisions identified 1248 projects in NIH Direct Operations which have been discontinued during the last ten to fifteen years, and this is known to be a considerable underestimate. Of this number 74% stopped because the objective of the project was completed, and 9% because the project proved unfeasible, unproductive or was rendered less important by developments in other fields. The projects as such were discontinued but a part of the work incorporated into other programs in 12 instances (1%). The remaining 16% of the projects ceased when the principal investigator left the NIH and funds for his support were redeployed to other urgent areas.

The Extramural Programs of NIH provide funds for almost half of the research in biomedical sciences in the Nation. In each of the last few years, NIH has received more than six thousand new applications for grants to support research in biomedical sciences in the Nation. In each of the last few years, NIH support and the NIH monies allowed funding of 80 to 90% of those for periods of two to seven years. If a grantee applies for renewal of an existing grant, he competes with new applications and his proposal is judged competitively with the latest concepts of scientists in his field. The decision on each project is based on the intrinsic scientific merit of the proposal, the accomplishments of the grantee

during the period of his existing grant and the degree to which the proposal coincides with the missions of the National Institutes of Health. In each of the last five years, 25% to 35% of the proposal renewals did not fulfill the criteria and support for the projects was discontinued.

EXAMPLES OF PROGRAMS DISCONTINUED

In the broadest view the programs of the NIH and its components can be seen to have expanded and then to have contracted and been discontinued in close parallel with the advancing frontiers of biomedical science. This can be traced from 1930 when at its establishment, the original National Institute of Health contained organizational "Sections" for Nutritional Diseases and Infectious Diseases, plus small Divisions for Pathology, Pharmacology, Chemistry, and Zoology.

Infectious diseases and immunology

The Section of Bacteriology studied bacterial diseases: tularemia, plague, and brucellosis. It also worked on rickettsial diseases like typhus and Rocky Mountain Spotted Fever. The Division of Zoology investigated the vermin which spread these diseases. With the advent of sulfonamides in the late 1930s and antibiotics in the 1940s, the focus moved to supporting large programs of research on treatment of specific diseases, for example, syphillis with penicillin and in the early 1950s, tuberculosis with streptomycin. While the chemotherapeutic conquest of bacterial and parasitic diseases decreased the relative importance of these diseases, new discoveries were emerging in research on viruses. During the 1950s, the programs for research on bacteria were cut back and new support provided for studies of viruses such as poliomyelitis, respiratory diseases, measles, etc. As each of these has reached a stage for widespread application support has been expanded and then discontinued or cut back to a level appropriate to the solution of long term problems. The NIH involvement with the control aspects of polio vaccines in the 1950s and with measles vaccine in the early 1960's are other examples of large programs which were mounted and then discontinued when the work was done.

In the mid 1950s research in immunologic disorders began to expand. Historically the roots of this work can be traced from studies on allergy and infectious diseases. The relevance has spread however into many other fields including organ transplantation, and "auto-immune diseases." In the late 1950s yet another field opened wide with the development of research methods for work with Mycoplasma, which are microorganisms intermediate between bacteria and viruses. Some studies with these organisms have reached the stage of application in the developmental work for vaccines. At the extreme frontier of work with infectious diseases are the "slow viruses" which were studied first in animal diseases and now show promise of relevance to certain human diseases.

The pattern has been and continues to be the same in all these fields: Initial studies lay the ground work. These continue throughout a period of expanded relevance to human disease. When possible there is further expansion to exploit these findings in the treatment of human diseases. Once a successful form of therapy is established and incorporated into medical practice or public health methods, the research base for that particular disease shrinks back to a level appropriate for dealing with unsolved problems.

From vitamins to molecular biology

Another pathway can be traced from the Section on Nutrition and the Division of Chemistry in the original National Institute of Health. In the 1930s new vitamins were being isolated and synthesized throughout the biomedical world at a rate averaging almost one a year, and much of the excitement in the biochemical and biomedical worlds centered in this field. Gradually in the decade from 1935 to 1945 the productive center of biochemistry moved to the study of "intermediary metabolism," that is, the hundreds of separate chemical reactions by which foods are used and small molecules of living organisms are transformed, one into another. All of these reactions are dependent upon biological catalysts, called enzymes, and the decade from 1945 to 1955 was characterized by the continued mapping of the intermediary metabolic pathways and increasing research on enzymes. During these two decades the NIH phased out its major

emphasis in nutritional studies and developed new programs for the study of enzymes and intermediary metabolites. It became world renowned in these fields and their application to the characterization of certain diseases.

In the mid and late 1950s the NIH began to cut back on these studies. The decade from 1955 to 1965 witnessed the onset of one of the great scientific syntheses in history: a combination of knowledge gained from the study of intermediary metabolism, of enzymes, of nucleic acids, of viruses, and of genetics. The result has been called "molecular biology." It is nothing less than an intimate description of the very large molecules which compose living organisms and the way in which new life is created, develops and is controlled. This rapid expansion of knowledge paralleled the general expansion of NIH support for biomedical research.

Other programs of therapy

One of the most dramatic discoveries of a therapeutic effect came just prior to 1950, when the adrenal hormone, cortisone, and the pituitary hormone which stimulates cortisone secretion were both shown to suppress symptoms of inflammation in rheumatoid arthritis and acute rhemumatic fever. For several years thereafter, NIH supported a highly coordinated program throughout the United States and in the United Kingdom to explore the usefulness of this effect and its limitations. The program was discontinued when these factors had been defined.

Toward the middle of the 1950s a promising lead appeared for the treatment of epilepsy with the amino acids, glutamine and asparagine. A program was organized to confirm this finding as rapidly as possible by the cooperative efforts of medical centers throughout the country. The beneficial effects proved not to hold for the great bulk of patients and the study was terminated as soon as the lack of general efficacy had been demonstrated.

In the late 1950s NIH set up a large, ambitious program to screen thousands of chemicals in experimental systems for their potential value in treating cancer, and to make promising compounds available to qualified investigators throughout the country. In addition to this fundamental work, coordinated programs were supported for the study of the therapeutic effect of selected drugs and combinations of drugs in the treatment of human cancer. Therapeutic studies of individual drugs, alone or in combination, have been discontinued as each defined the role of its particular treatment. The basic screening systems have been reprogrammed by discontinuing those which showed less value in selecting agents of value and identifying the animal models which predict human experience with reasonable accuracy.

Studies of disease causation and prevention

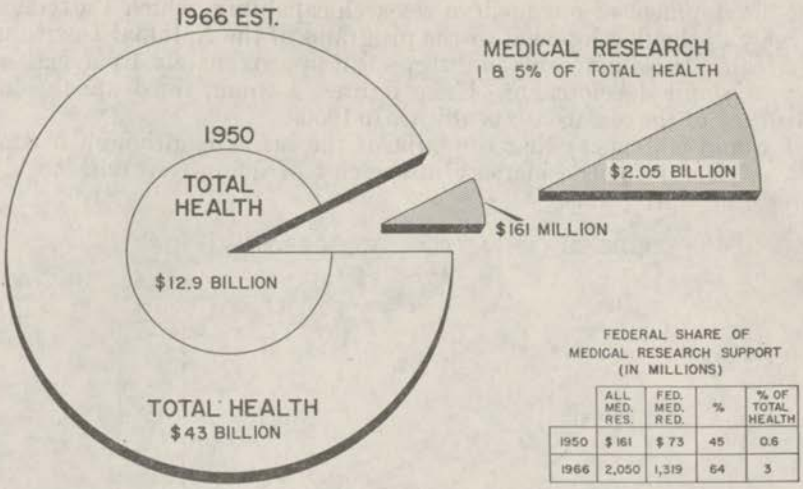
In the early 1950s a large program was organized to make use of the apparent value of the pattern of blood lipoproteins in detection of a predeliction for arteriosclerotic disease of the coronary arteries. It was shown that within the terms of the study this diagnostic approach had little value. It was discontinued and subsequently NIH undertook carefully planned large scale studies of the effects of diet on blood lipoproteins and coronary artery disease, and is now embarking upon coordinated studies of effect of alternative therapeutic regimens for patients with known coronary disease.

The early 1950s saw the successful completion of a large program of research to show how the basic cytodiagnostic test ("Pap smear") for uterine cancer could be applied on a mass population basis in different local communities. When this proved successful, the program was transferred to a different Bureau of the Public Health Service for nationwide implementation, and the NIH activity in the field was terminated.

In the late 1950s a coordinated NIH program demonstrated that the cause of the formation of scar tissue in the eyes of premature infants was the concentration and duration of the oxygen administered to support the infants during their early days of life. When this knowledge was developed to the point where it could be applied to decrease the incidence of the disease, retrolental fibroplasia, the program was discontinued.

In the 1960s NIH organized large epidemiologic studies to explore the relation of smoking to lung cancer and to uncover factors responsible for disorders in the normal development and delivery of human pregnancies. The primary phases of each of these programs are complete. The preliminary types of study have been terminated and the secondary phases of more specific definition of causation are underway.

MEDICAL RESEARCH AS A PROPORTION OF THE NATION'S HEALTH COST 1950-1966



FEDERAL SHARE OF MEDICAL RESEARCH SUPPORT (IN MILLIONS)

	ALL MED. RES.	FED. MED. RED.	%	% OF TOTAL HEALTH
1950	$161	$73	45	0.6
1966	2,050	1,319	64	3

COST OF DELIVERING MEDICAL SERVICES

Dr. SHANNON. I would like to turn to the next chart. As the Nation becomes increasingly preoccupied with medical care and as the Federal Government becomes incerasingly involved in medical care, it becomes important to view the research and development effort against the background of the cost of utilizing that information.

In industrial terms, this $43 billion—which is a rough calculation of the cost of medical services for all purposes during 1966—would be described as——

Mr. FLOOD. Medical services?

Dr. SHANNON. Delivery of medical services—medicine, hospitals, physicians' fees, paramedical personnel—the total cost of delivering medical care in the Nation is at the level of $43 billion.

Mr. FLOOD. Is that large?

Dr. SHANNON. $43 billion is a lot.

Mr. FLOOD. Even you think so?

Dr. SHANNON. Yes, sir, but I did not put that chart up to show that.

The point of this chart is to view medical care as though it were an industrial enterprise. Were this a corporate entity, you would equate the medical care costs here with income from sales, and you would equate medical research with expenditure for research and product development. Viewed in this sense, the medical care industry—which is a highly innovative industry like the pharmaceutical, aerospace, and the electronics industries, each of which has a major corporate commitment to research and development—would be expected to expend as much as 10 to 20 percent of its income from sales on research and

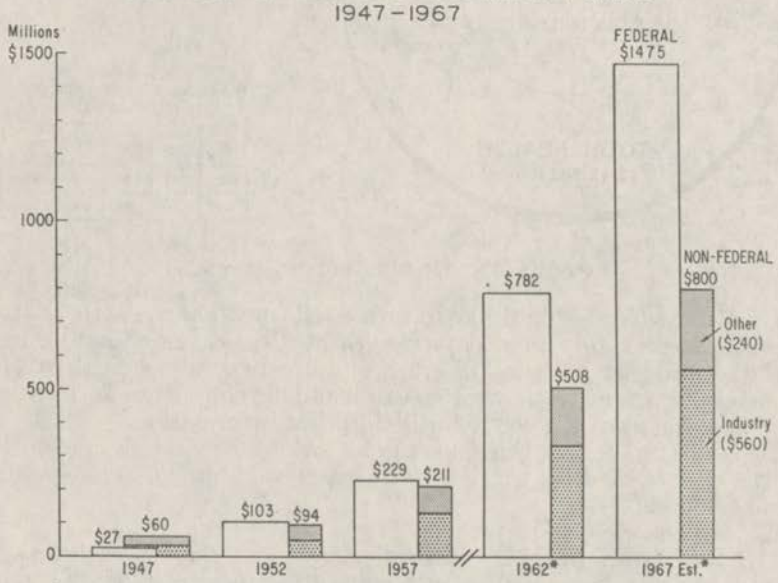
development. The aerospace industry actually spends a substantially higher percentage.

This chart shows that in the medical care industry, as I shall call it, slightly more than 5 percent of the sales dollars are devoted to the development of new knowledge and progress.

It is important to note that during the base year (1950) and before the development of our modern research capability, which I attribute largely to the development of the programs of the National Institutes of Health, this innovative industry spent approximately 1 percent for research and development. These figures, I think, illustrate the inadequacy of the research expenditure in 1950.

I would emphasize that the bulk of the increase, although it contains a factor for the increase in the cost of doing research, largely reflects new programs.

SOURCES OF MEDICAL RESEARCH FUNDS
1947-1967



*Non-Federal data are not strictly comparable with those for prior years, as coverage has been improved.

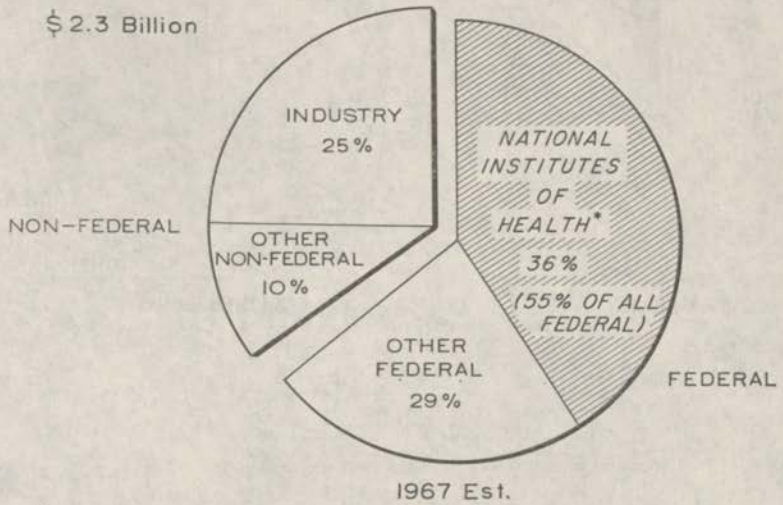
SOURCES OF FUNDING FOR MEDICAL RESEARCH

It is interesting in the fourth chart to look at the source of support funds. On the previous chart it was indicated that the proportion of research and development supported by the Federal Government was 45 percent—these were the figures in the lower right-hand corner—in 1950. In 1960, it was 64 percent.

This chart shows the change in the source of support from 1947 to the estimate for 1967. The 1947 figure was taken as the base year here simply because this chart had already been drawn for other purposes, and we found it simpler to bring the existing chart up to date than to redo the chart from scratch.

The chart shows the increase in support from all sectors of society—official, industrial, and private. Current Federal involvement in this function is 64 percent of the total.

NIH FUNDS AS A PROPORTION OF NATION'S MEDICAL RESEARCH SUPPORT



*Excludes National Institute of Mental Health (4%).

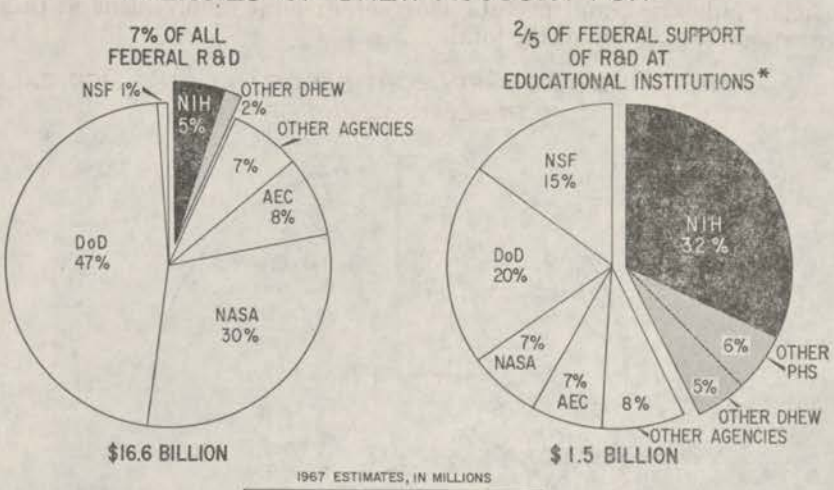
ROLE OF NIH IN SUPPORT OF MEDICAL RESEARCH

The more specific role of NIH in support of this function is portrayed in the next chart. Here you see that NIH accounts for 36 percent of the total, and this excludes the new bureau of Mental Health that was recently separated from NIH. The term "other Federal expenditures" includes funds of Mental Health, research elsewhere in the Public Health Service, and biomedical research in the Veterans' Administration, Department of Defense, AEC, Agriculture, and the National Science Foundation.

There are two other important features to this chart. The first is the large expenditure by industry in support of research and development from its own earnings. This chart shows that to be approximately 25 percent of the national total. Equally important is the very small contribution from other non-Federal sources, amounting to 10 percent, which includes institutional endowments, voluntary agencies, State and local governments.

If you look at the two pie diagrams in the next chart, a meaningful analysis is further made clear. First, all Federal research and development funds, which are estimated to be $16.6 billion in 1967 out of a total of $23 billion for the Nation as a whole, come from predominantly two sources—NASA and the Department of Defense, with NIH contributing only 5 percent of the total R. & D. funds. The AEC contributes 8 percent.

AGENCIES OF DHEW ACCOUNT FOR—



1967 ESTIMATES, IN MILLIONS

AGENCY	R&D	R&D IN ED. INST.
TOTAL FEDERAL	$16,602	$ 1,468
DHEW	1,161	625
PHS	1,018	556
NIH	814	477
NIMH	102	42
OE	81	57

*EXCLUDES UNIVERSITY-MANAGED FEDERAL-CONTRACT RESEARCH CENTERS

SUPPORT OF INSTITUTIONS OF HIGHER EDUCATION

The second diagram displays the support for institutions of higher education. The first diagram to the left is all research and development—industrial, educational or otherwise. The second is research within the educational enterprise. The striking difference here is, as you see, that NASA and the Department of Defense are not the dominant influences in support of research in the academic enterprise. They are replaced by a combination of NSF and the programs of the Department of Health, Education, and Welfare, which together amount to nearly 60 percent of the total. NIH alone accounts for 32 percent of this total.

Mr. FLOOD. I am surprised that the Defense figure is that low in the educational area. I had the idea that it was much higher than that.

Dr. SHANNON. Mr. Flood, if you take figures for the base year 1950, the Department of Defense was the dominant factor in educational institutions, but from 1950 on it becomes a decreasingly less important figure. Actually, the dollar value has not changed a great deal, but as the total R. & D. function expands, DOD becomes less important.

There is one feature that this chart does not display. The chart relates to research and development in association with the educational enterprise, but does not cover the contract laboratories that are separate from the educational enterprise, such as the Lincoln Laboratory, which is run by MIT, in electronics; the Lawrence Radiation Laboratory, which is run by the University of California, separately from the educational enterprise; it does not cover the jet propulsion laboratory which is run by Cal Tech as an independent enterprise;

nor does it cover the national laboratories that are run in loose association with the Atomic Energy Commission.

Mr. FLOOD. These operations are wholly owned subsidiaries of the educational institutions?

Dr. SHANNON. I would put it another way. They are wholly owned subsidiaries of the supporting agencies, and their programs are determined by the supporting agencies. In other words, I do not differentiate, in my own mind, the jet propulsion laboratory from any other directed activity of NASA, nor do I differentiate the national laboratories that are run by the Atomic Energy Commission from the program of the Atomic Energy Commission.

On the other hand, the Radiation Laboratory of the University of California, together with Brookhaven, are the two outstanding laboratories in the field of small-particle physics and, indeed, they constitute a very broad academic resource, although the operations are conducted external to the educational enterprise itself. They are used particularly for predoctoral thesis work and for postdoctoral experience.

The programs that are included in the diagram to the right of the chart are those programs that are contained within the departmental structure of our universities and professional schools, and constitute an intimate mix between education, on the one hand, and research and service, on the other.

EFFECT OF RESEARCH SUPPORT ON QUALITY TEACHING

Mr. FLOOD. The magnitude of the program that you are indicating raises the question in the educational world as to what extent you have prostituted these people. Are they doing research and forgetting about the student? Do they forget why they were there originally? These are very rich funds, you know.

Dr. SHANNON. I was about to comment on that. Viewed in that light, the picture that emerges is that the educational institutions receive, in toto, $1.5 billion for the support of research in all areas of science. These encompass the physical sciences and engineering, the biomedical sciences, and the behavioral sciences.

These funds are derived from five major agencies—HEW, NSF, DOD, NASA, AEC—and a variety of other agencies.

Mr. FLOOD. Yes, I know, Doctor. My point is, How can you get these professors out of the laboratory across the campus and bore him by lecturing the students?

Dr. SHANNON. Mr. Flood, I do not deny that at times it is difficult to engage a scientist with the prosaic business of teaching undergraduates. On the other hand, I do not believe that the separation of teaching and science is generally as portrayed to the public. I am convinced that the vitality and vigor of graduate education—where we are dealing not with the general education of the individual, but with the development of science, technology, and the like—are totally dependent upon broad support for the research function. The development of these people who are so essential to our economy, whether it be in terms of new knowledge for the medical sciences or new capabilities of an industrial nature—the ability of our society today to

develop these types of people depends wholly upon support for keeping this type of science activity firmly imbedded in the university structure.

I think two things are clear. One is the dependence of the universities on support from multiple sources. Realizing that in the biomedical sciences 65 percent of the support is from Federal and 25 percent from industrial——

Mr. FLOOD. Are we aware that there is a problem? I do not know whether there is or not, but it is being suggested more every year that there is.

Dr. SHANNON. You anticipate. I am trying to build up to make the point.

Unless one appreciates the extent of the dependence of science activity in the universities upon Federal programs, it is not apparent what obligation this carries for the Federal Establishment. I think the Federal Establishment, in a very real sense and in no small measure, determines the type of research that it will support and the terms and conditions that govern the availability of funds.

I think these factors have a dominant influence on the capability of institutions to define their own objectives and to develop programs that suit their needs and to continue as an independent intellectual resource for the Nation.

Mr. FLOOD. We are giving them so much, and they find their work intriguing and exciting, and properly so. I just hope that they are not so enamored with the research that they forget the mission of the university, which is also to teach.

Dr. SHANNON. Putting it another way, I think they are getting good support for research, but I think they are not getting good support for the educational function. I further feel that the terms and conditions under which this support is given them are not such as to facilitate their discharging their total responsibiliy.

Mr. FLOOD. But you have this problem: These fellows resent bitterly the presumption and impertinence of anyone who would want to audit and require that they account for the money that has been given them. We have given *x* dollars. The fact that strange, mundane characters would appear there in the guise of auditors and accountants annoys them no end.

Dr. SHANNON. I wish you had written my talk, because you are anticipating something I wanted to say. I wanted to comment on something that Congressman Smith said on Tuesday which relates precisely to this.

Mr. FLOOD. Go ahead.

EVOLUTION OF MANAGEMENT SYSTEMS AT NIH

Dr. SHANNON. As Congressman Smith said, a couple of committees of the House looked into this. As he said—and as I think even the people in NIH agree—partly due to the pressure caused by a series of substantial appropriation increases, NIH has not been able to give, or has not given, adequate attention to a number of management problems.

Then he asked Dr. Stewart if, at his level, he had done anything to help this problem. I do not think Dr. Stewart answered the ques-

tion in the context that Mr. Smith asked it, because Dr. Stewart's reply was in the context of the Wooldridge Report and Ruina Report, which dealt with broad program planning and management, and, more particularly in the Ruina Report, with engineering development. I believe Mr. Smith had reference to studies that were undertaken by the Government Operations Subcommittee, chaired by Congressman Fountain, I believe, in 1961.

Mr. SMITH. That is one of the reports, yes.

Dr. SHANNON. I would have to say that I must disagree with some of the implications contained in Mr. Smith's questions, and I would like to comment on them in terms of some of this background.

We did have problems in the evolution of management systems in the period 1956 through 1964 when budgets were increasing at a rate of approximately 30 percent a year. I think this was further complicated by what were usually late appropriations, as developed in discussions between the congressional committees. We have frequently had only 6 months, after apportionment, to obligate the funds, and rarely as long as 9 months. We still have some technical problems in the management of fellowships, research grants, and grants for training.

I do not believe, however, that anyone in the NIH has felt any compulsion due to "pressure caused by having to spend." I do believe that we have given as much attention as possible to the basic management problem. I would like to invite Congressman Smith, if he would, to visit with us and really see what the program amounts to.

The important thing is that subsequent to Congressman Fountain's hearings, a whole series of things have happened that have greatly complicated the life of the universities. While I agree with you in your statements on public accountability for public funds——

PUBLIC ACCOUNTABILITY FOR PUBLIC FUNDS

Mr. FLOOD. In the Defense area we give them so much money, and we found them cutting the grass, painting the lavatories, sweeping the floor, and all sorts of odds and ends. They had this money and they used it—so much for this and so much for that. A great deal of it did not go to what we intended at all.

Then when we went in with our auditors and accountants to say "This you can't do," there was quite a hue and cry that we were interfering with the freedom of the academic world, and all sorts of things.

Dr. SHANNON. Sir, I do not believe that you would get that hue and cry now, but I think you would get a different one that probably has more basis in valid fact.

Mr. FLOOD. This was several years ago.

Dr. SHANNON. We have moved, for example, from the calculation of overhead on a simple formula basis, which was known to be well below the actual overhead, to the very complex problem of cost participation, which involves some designated and verifiable contribution on the part of the institution.

We have limitations on expenditures by objectives. We have problems that relate to converting the terms and conditions of the grant-in-aid mechanism to the industrial type of time-or-effort reporting by participating scientists.

The problem here is that these scientists are not supported within the context of the administrative pattern of a single agency. I believe that if one is going to study the administrative pattern of a single agency, then one should also study the administrative pattern of the institutions that it supports: the medical schools and associated research institutions in the education and research function, the utilization of funds from various sources, and the multiple accounting mechanisms that are required by the different agencies. You will find that the scientist today has the attitude of a base runner who feels he is likely to be caught off base by his own accountant or a Federal auditor with no way to go.

Mr. FLOOD. I do not think that will take too many years off his life, do you?

Dr. SHANNON. I have two convictions: One, that these institutions are an essential national resource, and that the present mechanisms do not assure that they are utilized effectively. I concur with the President's view, as stated in his message to the Congress, that there must be a way of improving the quality of Government supervision insofar as this relates to the institutions they support. He has, indeed, set up a task force to see if certain simplifications are possible in the management of support programs which will provide strict accountability, on the one hand, on terms and conditions that are livable——

Mr. FLOOD. The Appropriations Committee of the House thought of that a long time ago.

MANAGEMENT PROBLEM OF MODERN RESEARCHERS

Dr. SHANNON. Take the scientist who has support from perhaps three agencies for different parts of a research problem and who is engaged in education, in research, and also in clinical service. When you try to allocate his time among his three primary functions—research, service, and education—this is relatively easy. When you try to split his research three ways, by source of support, it becomes almost impossible.

I was talking to Dr. Robert Felix, who was Director of the National Institute of Mental Health for many years and left us about 3 years ago to become dean of the St. Louis University School of Medicine. I suggested to him that it might be useful to the committee to have an old line Federal administrator, who did an extraordinarily effective job as an Institute Director from the creation of the Institute until the time of his retirement and who now is doing an equally effective job as the dean of a large and complex medical school, to discuss some of these problems with you as he views the Federal Government now, not from inside but from outside.

COMMENTS ON PROBLEMS OF PUBLIC ACCOUNTABILITY BY PRESIDENT OF YALE UNIVERSITY

If you have a mind to engage in such a discussion, I would strongly suggest another person who has thought very deeply about these problems, who has as righteous an attitude toward accountability as you, sir, but who feels that the multiple restrictions, due to funds from multiple Federal sources, are so dominant in the educational world at the present time as to make an investigator either live a very harried

existence or, perhaps, be very sloppy in his records so they do not really reflect his real life. This is Kingman Brewster, Jr., who is president of Yale University, a very thoughtful individual who has looked into this problem in great depth. I would be glad to make available to you, sir, if you would like to see it, a letter which he wrote to Dr. Leland Haworth, who is Director of the National Science Foundation. I think it states the problem as viewed from the vantage point of a responsible university administrator who views with conviction the essential nature of science in his establishment, but realizes the quandary the professions are in with the mutliple agencies involved.

Mr. FLOOD. I think you should put it in the record. In the early days there was negligence, blatant abuse, and sometimes deliberate evasion of the restrictions we tried to impose upon the academic world, that accompanied this sudden influx of gold. I can see why it startled them and why it was hard to handle, but it did happen. I think the worst is over, and there has been considerable improvement. From what you say, I think it is important to have this letter in the record to show the other side, also.

Dr. SHANNON. I think it states the problem, and I trust it will clarify the situation somewhat. The problem really stems from the quite different authorities under which the various Federal agencies operate. Ours happens to be very restrictive. The National Science Foundation's happens to be very general.

I think at the present time the restrictions are so many and so numerous as to defeat the very purposes of the support.

Mr. FLOOD. The pendulum can swing the other way, you know.

(The letter follows:)

YALE UNIVERSITY,
OFFICE OF THE PRESIDENT,
New Haven, Conn., December 23, 1966.

Dr. LELAND J. HAWORTH,
Director, National Science Foundation, 1800 G Street NW.,
Washington, D.C.

DEAR DR. HAWORTH: Yale is deeply concerned with increasing problems caused by directly charging portions of the salaries of academic faculty members to federally supported research grants.

The practice of charging such salaries directly is distasteful to many faculty members because they then feel responsible for raising part of their own salaries. Direct charging has also introduced a variety of administrative complications in the budgeting and accounting of academic salaries within the University. Moreover, the direct charging of "summer compensation" for those faculty on nine-month appointments often creates a divided sense of responsibility for summer activities. This arises from the assumption on the part of the faculty member that since he is paid by he must be working for the granting agency and not the University.

Despite these concerns, the obvious advantages to faculty members of increased opportunities for research and professional development create a compelling case for continued recovery through research grants of summer salaries and certain academic-year salary fractions as well. Without such support university science would be seriously retarded and the national interest would suffer accordingly.

However, the advent of required cost-sharing, which has been fulfilled at Yale in the overwhelming majority of instances by "pledging" appropriate fractions of more stringent effort-reporting requirements to substantiate these "pledges" in accounting terms, have enormously increased the disadvantages of present practice. Administratively, the difficulties of accounting for the time of individuals, grant by grant, in blocks of charged time, required cost-sharing time, and additional time "contributed but not auditable" have not been resolved to our satisfaction. Nor are we aware of any university where they have been

dealt with satisfactorily. More importantly, we see deleterious effects on the university atmosphere and on the relationship between the universities and the agencies which generously support research—effects which seem likely to increase.

We would not want to give up, nor do we believe it is the policy of the Foundation or the Federal Government as a whole that we should give up, the increased quantity and quality of research and of earned doctorates in the sciences to which research grant support of faculty has so greatly contributed. But we believe that a new mechanism which preserves the advantages of the present one without all of its difficulties is badly needed.

Accordingly, we are prepared to propose to the Yale Corporation the following institutional agreement between Yale and the Foundation as an alternative to present practice.

1. Effective upon agreement with the Foundation, Yale will not incorporate either academic-year or summer salaries for the four instructional faculty ranks in its research proposals to the Foundation.

2. At the time each proposal is submitted, Yale will furnish by separate document approximate estimates of the probable effort of the faculty member(s) to be devoted to the research.

3. Three times each year, Yale will obtain from each member of the four instructional faculty ranks who devoted effort to research supported by NSF research grants a signed statement of the percentage of effort devoted to such research in the period just past, as follows:

(*a*) For faculty on a nine-month academic-year appointment, statements will be obtained at the end of each academic semester and at the end of the three-month summer period. The maximum declarable research effort for faculty carrying a normal teaching load is fifty percent during the nine-month academic year and one hundred percent during two summer months (corresponding to two-ninths of academic year salary).

(*b*) For faculty on an eleven-month academic-year appointment (the School of Medicine), statements will also be obtained at the end of the fall and spring semesters and at the end of the summer period. The maximum declarable research time will vary depending on terms of appointment in the School of Medicine.

4. At appropriate times each year, Yale will then make application to the Foundation for a block grant in support of faculty salaries, computed in amount by summing the certified fractions of salaries for the period just ended, adding predetermined percentages for fringe benefits and indirect costs, and deducting a negotiated percentage which would represent a contribution by Yale toward support of the research.

We believe this proposal would have three major advantages over present practice. First, it will eliminate dependence upon precise estimates of effort in advance, which are often unreliable and which are particularly irritating to faculty. It will also lengthen the estimating periods and break them logically by activity, which we believe will produce both more even and more reliable estimates.

Second, by separating salary charges from individual grants, it will alleviate a variety of felt problems within the scientific community, and a host of administrative difficulties.

Third, and not least important, it will affirm the university's full responsibility for salary administration, winter and summer.

We would welcome your comments and the opportunity to discuss this proposal further with you.

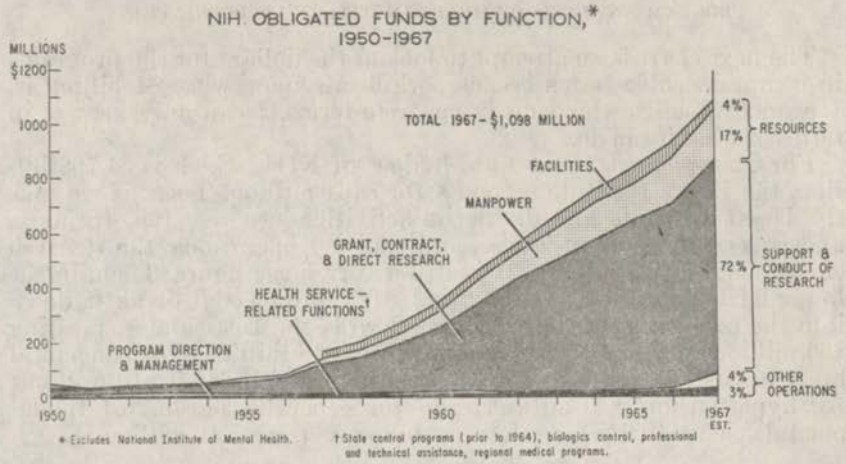
Sincerely yours,

KINGMAN BREWSTER, Jr., *President*.

RATE OF NIH GROWTH

Dr. SHANNON. Mr. Chairman, the next chart shows the rate of growth of the National Institutes of Health since 1950. I think it has been rapid but orderly. It shows the progressive acquisition of new functions.

There are basically four periods that one can speak to. Up to 1950, it was the establishment of the modern programs at the National Institutes of Health.

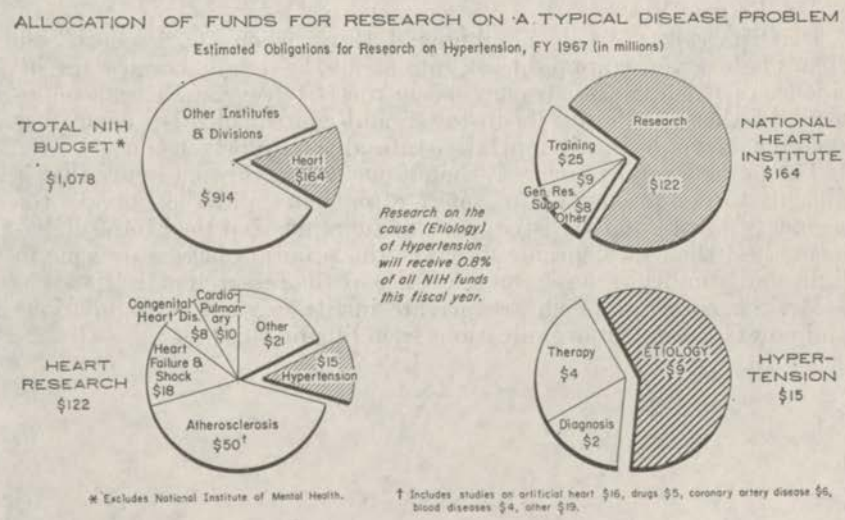


From 1950 to 1955 was a holdback period, due to the Korean war, and a period of refinement of mechanisms.

From 1956 through 1960 was the period of large general program increases, with the establishment of broader training programs and construction programs and institutional support programs.

Then from 1960 to 1965 we began sorting out the programs that required special attention.

Our present budget will show that in the grant area this year the increase in research grants is approximately 8 percent. In the training area it is substantially less. The big increase represents the emergence of the regional medical program which is the only medical service component in our operation.



PROGRAM ANALYSIS OF HEART INSTITUTE APPROPRIATIONS

The next chart is an attempt to look at the dollars for the programs in comprehensible terms because, while we know what $1 billion is, I cannot visualize this sum in concrete terms. I can only view it in terms of what it can do.

For example, out of the total budget of NIH, which is $1.708 billion, the Heart Institute accounts for $164 million. Then, if we take the Heart Institute and divide its activities into research, training, and general support programs and contract operations, the research component is $122 million. It is still a very large figure. Then, in the lower lefthand corner, we take that $122 million and break it down into the problem areas. For atherosclerosis the Institute is spending $50 million; for heart failure and shock, $18 million; for congenital heart disease, $8 million; for cardiopulmonary diseases, $10 million; for hypertension, $15 million; and for general programs of fundamental science that have relevance to many areas, $21 million.

HYPERTENSION

Mr. FLOOD. What is hypertension?

Dr. SHANNON. High blood pressure.

Mr. FLOOD. What does that mean?

Dr. SHANNON. Well, we normally find blood pressure about 120 or 130 over 80 in terms of the column of mercury.

Mr. FLOOD. Why is it serious? So I have high blood pressure. What difference does it make?

Dr. SHANNON. It causes headaches, cardiac disability, and death. In connection with atherosclerosis it causes stroke. Seventeen million Americans between the ages of 18 and 79, which is 15 percent of the adult population, have definite hypertension.

Mr. FLOOD. Why?

Dr. SHANNON. We do not know. I think when Dr. Frederickson comes before you you might ask him about the details because the incidence of this disease has changed in the last 10 years. The development of therapeutic agents to lower and control blood pressure has caused a sharp decline in mortality rates due to hypertension.

The point I want to make is that if one breaks down a figure that is difficult to comprehend into concrete segments and then breaks the segments down into the distribution of functions and then into subsegments and then into specific diseases, the program begins to come to light and you begin to see the relevance of the research activities.

Mr. SMITH. How much are private institutes such as foundations and non-Government organizations spending on this?

Dr. SHANNON. I am sure Dr. Frederickson can give a precise figure but in terms of all of the medical research in the Nation, a combination of all private agencies and endowments contribute about 10 percent of the total.

Mr. SMITH. Is it insignificant?

Dr. SHANNON. Well, sir, relatively small.

This presentation was to give you some idea of the scope of our operations.

Mr. FLOOD. Anybody who can talk as well as you can should not read a script.

Dr. SHANNON. I am more than a little emotionally involved in this and have been for some while.

Mr. FLOOD. You are not a very emotional type, at least not demonstrably.

I have some general questions to ask you. I will not go into details until we get to the individual institute directors.

GUIDELINES USED IN ARRIVING AT BUDGET ESTIMATE

Were any general guidelines used in arriving at the amount of the 1968 budget for your Institutes? What kind of guidelines did you use?

Dr. SHANNON. Well, in the initial preparation of the budget, Mr. Flood, we were asked to be reasonable and hardheaded and asked to realize——

Mr. FLOOD. Who asked you to be reasonable and hardheaded?

Dr. SHANNON. The Department.

Mr. FLOOD. Did the Secretary ask you to be reasonable and hardheaded?

Dr. SHANNON. Through Mr. Kelly, yes.

Mr. FLOOD. Did they say "keep off the grass" or "keep off the grass positively"?

Dr. SHANNON. No, sir, they said precisely what I have stated, and the interesting thing is that in their initial submission to the Bureau of the Budget they included most of our requests. Obviously it was their feeling that our requests were not inordinate.

Mr. FLOOD. What are the guidelines?

Dr. SHANNON. I do not think we had specific guidelines, did we, Mr. Cardwell?

Mr. CARDWELL. No. Generally we indicated to all our operating agencies and the National Institutes of Health that this would be a tough budget year and that they should be prepared to rank their requirements by priority.

Mr. FLOOD. Did you ask them to read the election returns?

Mr. CARDWELL. In effect we did, yes.

Mr. LAIRD. Did they rank all their programs and requirements by priorities? This is a new thing. I am glad to hear this but this is the first time it has been done.

Mr. CARDWELL. We developed two budget levels this year. One was in keeping with an extraordinarily tight budget. We presented this to the Bureau of the Budget and to the President. We also developed a second budget which in the Secretary's view would, if the President could identify additional funds, reach into areas of higher priority. We did this for each operating agency and for the National Institutes of Health.

Mr. FLOOD. That is good.

Mr. LAIRD. It is very good. I hope we can see the guidelines.

Mr. FLOOD. That is a real guideline.

HIGH AND LOW BUDGET FOR EACH APPROPRIATION OF THE DEPARTMENT

Mr. LAIRD. Can we have that priority list submitted for all programs of the Department and have it put in the record, Mr. Chairman?

Mr. FLOOD. Yes.

(The information referred to follows:)

Summary of high and low dollar budgets, fiscal year 1968

FOOD AND DRUG ADMINISTRATION

[Dollars in thousands]

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies		
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation	
Salaries and expenses	$96,252	$76,100	$82,231	$69,000	$66,749	−$9,351	Medical evaluation	$1,470
							Scientific research and evaluation	2,220
							Regulatory compliance	2,858
							Drug abuse control	2,373
							Executive direction and administration support	430
							Total	9,351
Building and facilities	22,000	2,200	2,200	3,150	1,150	−1,050	Veterinary research institute	1,100
							FB-8 laboratory space conversion	800
							Special pharmacological animal laboratory expansion	100
							Bureau of the Budget reduction (gross)	2,000
							Bureau of the Budget increase (gross): Laboratory No. 2 planning	950
							Net, Bureau of Budget reduction	1,050
Total	118,252	78,300	84,431	72,150	67,899	−10,401		

Summary of high and low dollar budgets, fiscal year 1968—Continued

OFFICE OF EDUCATION

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
Elementary and secondary educational activities:							
Educationally deprived children	$2,441,362	$1,529,254	$2,441,362	$1,448,000	$1,200,000	−$329,254	Provides nominal increase over total 1967 spending level and annualizes new programs for migrants, delinquents, and dependent children. Most increases due to formula changes are not funded.
Supplementary educational centers and services	865,000	225,000	487,000	200,000	240,000	+15,000	Increases number of new projects from 200 to 400.
Guidance, counseling, and testing	42,000	24,500	30,000	24,500	24,500		
Strengthening State departments of education	63,600	36,750	58,300	34,500	29,750	−7,000	Maintains 1967 level of support.
Equipment and minor remodeling	301,000	63,200	92,000	88,200	50,000	−13,200	Eliminates about 13,000 projects to acquire instructional materials and equipment.
Library resources		105,000	150,000	105,000	105,000		
Teacher training institutes	67,500	47,250	57,250	47,250	42,750	−4,500	Eliminates about 50 institutes for teachers.
Total	3,780,462	2,030,954	3,315,912	1,947,450	1,692,000	−338,954	
School assistance in federally affected areas:							
Maintenance and operations:							
Payments to local educational agencies.	391,909	358,540	389,200	391,700	389,200	+30,660	Adds funds required to maintain program at 1967 level.
Payments to other Federal agencies.	27,000	24,500	27,000	24,500	27,000	+2,500	
Construction:							
Assistance to local educational agencies.	47,380	39,380	39,380	39,380	12,317	−27,063	Reduced to 1967 level; does not cover backlog of projects authorized in 1967.
Assistance for school construction on Federal properties.	10,000	10,000	10,000	10,000	10,000		
Technical services	620	620	620	620	620		
Total	476,909	433,040	466,200	466,200	439,137	+6,097	

National Teacher Corps	50,000	37,875	46,000	25,000	36,000	−1,875	Supports 2,500 new members.
Higher Education Activities:							
Program assistance:							
Strengthening developing institutions.	55,000	30,000	50,000	30,000	30,000	----------	
Colleges of arriculture and mechanic arts.	11,950	11,950	11,950	11,950	11,950	----------	
Undergraduate instructional equipment and other resources.	70,000	14,500	47,500	14,500	14,500	----------	
Construction:							
Public community colleges and technical institutes.	112,200	88,660	107,800	99,660	89,700	+1,040	Provides additional funds to cover changes in legislation.
Other undergraduate facilities	397,800	314,340	382,200	353,340	300,300	−14,040	Estimates 40 construction projects.
Graduate facilities	90,000	60,000	90,000	60,000	50,000	−10,000	Eliminates 10 construction projects.
State administrative expenses	7,000	7,000	7,000	1,000	7,000	----------	
Technical services	4,000	2,744	4,000	2,744	2,744	----------	
Teacher education:							
Elementary and secondary teacher programs:							
Fellowships	122,000	48,010	83,000	43,010	27,500	−20,510	Reduces new fellowships from 4,560 to 3,215; provides less for continuation costs.
Strengthening graduate schools	7,500	5,000	7,500	5,000	7,500	+2,500	Provides grants to 185 institutions instead of 120.
College teacher fellowships	107,300	98,100	107,300	98,100	96,600	−1,500	Eliminates increase in dependency allowances.
Institutes in use of equipment and other teaching aids.	5,000	2,500	5,000	2,500	2,500	----------	
Student aid:							
Educational opportunity grants	184,000	179,618	184,000	174,500	159,600	−20,018	Reduces new awards from 145,000 to 121,000 and provides less funds for continuation costs.
Direct loans	153,000	150,000	198,400	192,000	193,400	+43,400	Funds added to bring program to 1967 level.
Insured loans	136,100	79,100	136,100	50,000	40,000	−39,100	
Work-study programs	219,900	146,600	171,600	146,600	139,900	−6,700	
Total	1,682,750	1,238,122	1,593,350	1,284,904	1,173,194	−64,928	
Expansion and improvement of vocational education:							
Vocational Education Act of 1963:							
Vocational training	418,000	138,736	134,625	134,625	138,736	----------	
Construction of area vocational education facilities		61,657	67,875	63,600	60,573	−1,084	Reduces support for construction projects.
George-Barden and supplemental acts:							
George-Barden Act:							
Practical nurse training	5,000	5,000	5,000	5,000	5,000	----------	
Area vocational training	15,000	15,000	15,000	15,000	15,000	----------	
Other vocational training	29,686	29,686	29,686	29,686	29,686	----------	
Supplemental acts	305	305	305	305	305	----------	
Appalachian regional development	7,000	----------	7,000	----------	7,000	+7,000	Continues program at about 1967 level; requires extension legislation.
Student aid:							
Insured loans	6,100	6,100	6,100	6,100	3,600	−2,500	Eliminates advances to reserve funds and direct loans.
Work-study programs	35,000	10,000	10,000	10,000	----------	−10,000	Phases out program which is to be absorbed by Neighborhood Youth Corps under Office of Economic Opportunity.
Total	516,091	266,484	275,591	264,316	259,900	−6,584	

Summary of high and low dollar budgets, fiscal year 1968—Continued

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
Libraries and community services:							
Library services	$52,500	$30,000	$52,500	$37,500	$40,815	+$10,815	Provides more funds for new programs added in legislative amendments.
Construction of public libraries	45,000	30,000	45,000	40,000	27,185	−2,815	Reduces number of projects from 350 to 330.
College library resources	50,000	25,000	50,000	25,000	25,000	----------	
Acquisition and cataloging by Library of Congress.	7,770	7,770	7,770	7,770	4,000	−3,770	Reduction in cataloging of library materials.
Librarian training	11,250	8,250	8,250	8,250	8,250	----------	
University community service programs.	50,000	20,000	30,000	20,000	16,500	−3,500	Reduces number of projects from 1,000 to 825.
Adult basic education	58,500	30,000	58,500	30,000	44,200	+14,200	Provides for 346,000 participants instead of continuing 1967 level of 270,000.
Total	275,020	151,020	252,020	168,520	165,950	+14,930	
Educational improvement for the handicapped:							
Preschool and school programs	50,000	50,000	50,000	50,000	15,000	−35,000	Reduces program level to serve 100,000 handicapped children instead of 330,000.
Teacher education	35,000	24,500	34,000	24,500	24,500	----------	
Research and demonstrations	18,000	11,100	12,000	11,100	11,100	----------	
Captioned films for the deaf	5,000	5,000	5,000	5,000	2,800	−2,200	Reduces program to 1967 level.
Total	108,000	90,600	101,000	90,600	53,400	−37,200	
Research and training:							
Educational laboratories and research and development centers:							
Operational assistance	86,000	50,500	53,000	29,600	36,100	−14,400	Reduces level of support to minimum continuation of labs and centers.
Construction	30,000	----------	27,600	----------	----------	----------	
Research:							
General education:							
General education research	46,350	19,300	21,350	18,085	18,850	−450	Provides slight increase in funds for new projects.
Evaluation studies	2,500	2,500	2,500	2,500	2,500	----------	
National achievement study	2,000	2,000	2,000	2,000	2,000	----------	
Demonstration and development.	70,000	3,000	36,000	3,000	3,000	----------	
Vocational education	22,500	22,025	22,500	22,025	17,100	−4,925	Reduces program to 1966 level.
Foreign language education	3,000	3,000	3,000	3,000	3,000	----------	
Educational media	4,400	4,400	4,400	4,400	4,400	----------	
Library improvement	3,550	3,550	3,550	3,550	3,550	----------	
Training	25,000	10,000	20,000	10,000	7,000	−3,000	Do.
Dissemination	3,200	3,200	3,200	3,200	2,400	−800	Do.
Total	298,500	123,475	199,100	101,360	99,900	−23,575	

Educational research (special foreign currency):							
Research in foreign education	1,800	765	1,800	500	1,800	+1,035	Provides for expanded support for foreign studies.
Training, research, and study grants	2,800	1,035	2,800	500	2,800	+1,765	
Total	4,600	1,800	4,500	1,000	4,500	+2,800	
Salaries and expenses	62,082	43,769	47,236	40,253	40,253	−3,516	Reduction primarily in studies and contracts.
Student loan insurance fund	----------	----------	----------	----------	----------	----------	
Higher education loan fund:							
Participation sales insufficiencies	3,200	3,200	3,200	3,200	2,625	−575	Reflects more recent estimate of need for interest insufficiencies.
Loans	200,000	100,000	100,000	----------	----------	−100,000	Offset by increase in participation sales.
Grand total	7,457,614	4,520,339	6,404,209	4,392,803	3,966,959	−553,380	

VOCATIONAL REHABILITATION ADMINISTRATION

Grants for rehabilitation services and resources:							
Vocational rehabilitation services	301,000	287,000	287,000	287,000	287,000	----------	
Innovation in rehabilitation services	5,000	4,000	5,000	4,000	3,200	−800	Reduction of 75 new grants.
Statewide planning grant	----------	----------	----------	----------	----------	----------	
Expansion grants	9,000	9,000	9,000	7,000	7,500	−1,500	Reduction of 33 new grants.
Construction of facilities and workshops	9,000	7,000	9,000	7,000	3,850	−3,150	Phaseout of State planning grants and reduction of 26 construction and initial staffing grants.
Workshop improvement grants	6,000	6,000	6,000	5,000	4,000	−2,000	Reduction of 80 new grants.
Training service grants	8,000	4,500	8,000	4,500	6,000	+1,500	Increase of 15 new grants.
Subtotal	338,000	317,500	324,000	314,500	311,550	−5,950	
Research and training:							
Research and demonstrations	29,334	24,578	24,578	21,514	21,850	−2,728	Reduction of 50 new grants.
Training	39,800	37,300	39,750	34,810	32,534	−4,766	Reduction of 641 new grants.
Special center program	11,650	11,300	11,650	11,300	10,950	−350	Reduction of 2 new grants.
International research (domestic support)	200	100	200	100	100	----------	
National study of rehabilitation needs	----------	----------	50	50	50	+50	
Subtotal	80,984	73,278	76,228	67,774	65,484	−7,794	
Research and training (special foreign currency program)	5,000	4,000	5,000	3,000	5,000	+1,000	
Grants for correctional rehabilitation study	800	800	800	800	800	----------	
Salaries and expenses	6,663	5,864	6,558	5,864	5,621	−243	18 new positions not allowed.
Total	431,447	401,442	412,586	391,938	388,455	−12,987	

Summary of high and low dollar budgets, fiscal year 1968—Continued

PUBLIC HEALTH SERVICE—SUMMARY BY BUREAU

[Budgetary estimates for the Public Health Service were developed under the old PHS organization structure up until Presidential reveiw; these tables are an attempt to reconstruct various estimates on the basis of categories used in the President's budget—and therefore contain some artificial delineations]

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
Health Manpower	$437,210	$354,428	$435,810	$342,000	$373,413	+$18,985	
Disease Prevention and Environmental Control	270,689	232,492	258,939	177,280	222,680	−9,812	
Health Services	508,314	391,754	500,910	459,511	440,731	+48,977	
NIH-NIMH	1,928,233	1,463,272	1,786,563	1,529,319	1,534,159	+70,887	
Other PHS	338,961	253,703	257,306	229,121	226,435	−27,268	
Total PHS (exclusive of Indian health programs)	3,483,407	2,695,649	3,239,528	2,737,231	2,797,418	+101,769	

PUBLIC HEALTH SERVICE

BUREAU OF HEALTH MANPOWER							
Health manpower education and utilization	218,210	148,928	216,810	176,000	170,413	+21,485	1. Research grants ..... +$534 2. Training grants: a. Dental ..... −1,300 b. Nursing: (1) Traineeships ..... −1,000 (2) Research training ..... −144 (3) Payment to diploma schools of nursing ..... −3,000 c. Public health traineeships ..... −1,000 d. Grants to schools of public health ..... −300 e. Project grants for public health training ..... −1,500 f. Educational improvement grants for health professions ..... +22,500 g. Allied health manpower ..... −4,050 3. Fellowships ..... −137 4. Student loans ..... +14,000 5. Direct operations ..... −3,118
Construction of health educational facilities	219,000	205,500	219,000	166,000	203,000	−2,500	Construction of teaching facilities for allied health professions personnel.
Total, Bureau of Health Manpower	437,210	354,428	435,810	342,000	373,413	+18,985	

BUREAU OF DISEASE PREVENTION AND ENVIRONMENTAL CONTROL								
Chronic diseases	43,302	32,575	36,065	20,000	27,942	−4,633	Research grants	−777
							Fellowships	−650
							Chronic diseases	−149
							Smoking and health	−1,712
							Diabetes and arthritis	−156
							Heart disease control	−519
							Respiratory diseases	−509
							Neurological and sensory diseases	−565
							Preventive services	−1,653
							Kidney diseases	+2,057
Communicable diseases	82,917	66,053	80,817	48,600	72,272	+6,219	Communicable diseases	−977
							Tuberculosis control	−217
							Venereal disease control	−961
							Foreign quarantine	−84
							Pesticides	−3,448
							Aedes aegyptieradication	+11,906
Air pollution	64,185	59,385	64,185	59,400	64,185	+4,800	President's budget at authorized ceiling (including proposed construction planning funds for an air pollution research center)	
Urban and industrial health	61,006	57,558	60,231	37,000	42,594	−14,964	Research grants	−923
							Training grants	+679
							Planning grants	+600
							Demonstration grants	−1,600
							Injury control	−8,160
							Arctic health research	−380
							Solid wastes	−544
							Food and water quality	−2,450
							Occupational health	−400
							Other direct operations	−1,786
Radiological health	19,279	16,921	17,641	12,280	15,687	−1,234	Research grants	−49
							Direct operations	−1,185
Total, Bureau of Disease Prevention and Environmental Control	270,689	232,492	258,939	177,280	222,680	−9,812		
BUREAU OF HEALTH SERVICES								
Community health services	104,266	63,260	98,148	70,000	68,523	+5,263	Research grants	+1,464
							Training grants	−600
							Mental retardation facilities construction grants	+10,000
							Direct operations	−5,601
Hospitals and medical care	75,213	67,145	73,927	70,676	63,851	−3,294	Inpatient-outpatient care	−2,792
							Construction guard	−216
							Health units	−286
Hospital construction activities	328,835	261,349	328,835	318,835	308,357	+47,008	Hill-Burton general hospital construction	+30,000
							Appalachian demonstration health facilities	+15,000
							Hospital facilities research	+2,486
							Direct operations	−478
Total, Bureau of Health Services	508,314	391,754	500,910	459,511	440,731	+48,977		

Summary of high and low dollar budgets, fiscal year 1968—Continued

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
NATIONAL INSTITUTES OF HEALTH							
Grants:							
Research	$721,586	$601,850	$694,503	$639,757	$644,489	+$42,639	In contrast to other PHS accounts which are broken down by appropriation and which identify differences between PHS low and 1968 President's budget in terms of activity, NIH-NIMH are broken down by activity, and differences between PHS low and 1968 President's budget in terms of activity can be identified by looking to the stub column.
Training programs	205,223	190,781	205,223	200,000	194,597	+3,816	
Regional medical programs	197,000	52,000	135,000	68,000	59,400	+7,400	
Total grants	1,123,809	844,631	1,034,726	907,757	898,486	+53,855	
Direct operations:							
Laboratory and clinical research	93,353	87,433	86,538	84,083	81,691	−5,742	
Collaborative research and development	120,124	119,098	124,146	119,098	113,037	−6,061	
All other direct operations	65,669	42,460	63,701	41,140	59,036	+16,576	
Total, direct operations	279,146	248,991	274,385	244,321	253,764	+4,773	
Subtotal, National Institutes of Health	1,402,955	1,093,622	1,309,111	1,152,078	1,152,250	+58,628	
Grants for construction of health research facilities	115,000	65,000	100,000	50,000	35,000	−30,000	
Grand total, National Institutes of Health	1,517,955	1,158,622	1,409,111	1,202,078	1,187,250	+28,628	
NATIONAL INSTITUTE OF MENTAL HEALTH							
Research grants	83,917	71,631	81,680	73,499	76,477	+4,846	
Hospital improvement grants	13,610	10,610	13,610	10,610	10,610	----------	
Training programs	110,111	92,467	115,568	108,647	110,621	+18,154	
Direct operations	61,065	45,667	49,519	47,782	49,033	+3,366	
Construction of community mental health centers	80,000	50,000	60,000	50,000	50,000	----------	
Mental health staffing	61,575	34,275	57,075	36,703	50,168	+15,893	
Total, National Institute of Mental Health	410,278	304,650	377,452	327,241	346,909	+42,259	
Grand total, National Institutes of Health-National Institutes of Mental Health	1,928,233	1,463,272	1,786,563	1,529,319	1,534,159	+70,887	

OTHER PHS								
National health statistics	10,031	9,798	9,931	8,798	9,767	−31	Lapse increase	−$31
National Library of Medicine	30,279	26,308	29,279	23,386	21,162	−5,146	Grants:	
							Research	−1,400
							Training	−150
							Construction	−2,500
							Publication and library support	−700
							Direct operations	−396
							Total	−5,146
Scientific activities overseas	18,685	18,685	18,685	10,000	18,685			
Retired pay of commissioned officers	13,391	13,391	13,391	13,391	13,391			
Comprehensive health planning and services	145,001	145,001	145,001	145,001	143,628	−1,373	Review and approval	−500
							Program direction and technical assistance	−873
							Total	−1,373
Office of the Surgeon General, salaries and expenses	10,659	10,659	11,115	10,222	9,087	−1,572	International health activities	−207
							Management and control services	−1,365
							Total	−1,572
Buildings and facilities	110,915	29,861	29,904	18,323	10,715	−19,146	Communicable disease center addition	−1,241
							Animal breeding and holding facility, CDC	−176
							Southeast radiological health laboratory	−203
							Northeast shellfish sanitation research center	−190
							NIH animal center	−7,512
							Combined service facility, NIH	−168
							International conference building	−410
							NIH multilevel parking facility	−110
							NIH incinerator facility	−1,190
							Modernization of PHS hospitals	−4,134
							National Library of Medicine Annex	−290
							Headquarters building, PHS	−2,400
							Repairs and improvements	−1,122
Total, other PHS	338,961	253,703	257,306	229,121	226,435	−27,268	Total	−19,146

Summary of high and low dollar budgets, fiscal year 1968—Continued

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
ST. ELIZABETHS HOSPITAL							
Salaries and expenses	$37,674	$35,266	$35,266	$35,266	$35,140	−$126	Represents reduction in travel, supplies, summer employment, and miscellaneous.
Buildings and facilities	10,130	9,920	9,920	1,237	1,237	−8,683	Deferral of request for construction funds for a new security facility because construction contract could not be awarded until 1969. In 1966 an amount of $25,000 was made available to prepare a program statement for this project and the 1967 appropriation included $450,000 for architectural and engineering planning. It is expected that plans will be approved in June 1968.
Subtotal	47,804	45,186	45,186	36,503	36,377	----------	
Less reimbursements	−26,276	−26,167	−26,167	−26,167	−26,096	----------	
Total, St. Elizabeths	21,528	19,019	19,019	10,336	10,281	----------	
SOCIAL SECURITY ADMINISTRATION							
Payment to trust funds for health insurance for the aged.	928,592	1,001,592	1,001,592	1,001,592	906,631	−94,961	Deleted from fiscal year 1968 budget and requested in fiscal year 1967 supplemental.
Payments for military service credits	126,000	126,000	126,000	126,000	105,000	−21,000	Revised estimate.
Total	1,054,592	1,127,592	1,127,592	1,127,592	1,011,631	−115,961	
WELFARE ADMINISTRATION							
Grants to States for public assistance	4,240,000	4,240,000	4,240,000	4,240,000	4,240,000	----------	
Assistance for repatriated U.S. nationals	525	525	525	525	525	----------	
Bureau of Family Services, salaries and expenses.	9,653	9,346	9,653	9,346	8,589	−757	Reduction of 51 new positions.
Grants for maternal and child welfare:							
(a) Maternal and child health services	55,000	55,000	55,000	55,000	50,000	−5,000	Reduction maintains 1967 level.
(b) Crippled children's services	55,000	55,000	55,000	55,000	50,000	−5,000	Do.

(c) Child welfare services	55,000	55,000	55,000	55,000	46,000	−9,000	Do.
(d) Research, training, or demonstration projects in child welfare.	12,000	10,508	12,000	10,508	10,200	−308	Eliminates 54 training grants.
(e) Special project grants for maternity and infant care.	30,000	30,000	30,000	30,000	30,000	----------	
(f) Special project grants for health of school and preschool children.	40,000	40,000	40,000	40,000	40,000	----------	
(g) Training of professional personnel for the care of crippled children.	10,000	10,000	10,000	10,000	7,000	−3,000	Eliminates 7 new projects.
(h) Research projects relating to maternal and child health and crippled children's services	7,000	6,520	7,000	6,520	6,120	−400	Difference in estimates of amount necessary to fund continuation costs.
Subtotal	264,000	262,028	264,000	262,028	239,320	−22,708	
Children's Bureau, salaries and expenses	7,088	6,965	7,088	6,965	6,485	−480	Reduction of 29 new positions.
Cooperative research or demonstration projects.[1]	4,470	4,470	4,470	4,470	4,170	−300	Reduction of 6 new research grants.
Research and training (special foreign currency program).	2,500	1,500	2,500	1,500	1,500	----------	
Office of the Commissioner, salaries and expenses.	2,129	2,129	2,129	2,129	1,888	−241	Reduction of 16 new positions.
Assistance to refugees in the United States	53,500	53,500	53,500	53,500	53,500	----------	
Total	4,583,865	4,580,463	4,583,865	4,580,463	4,555,977	−24,486	
ADMINISTRATION ON AGING							
Coordination and development of programs for the aging:							
Grants for community planning, service, and training.	15,000	11,000	15,000	13,104	10,550	−450	Reduction of 50 new grants.
Grants and contracts for research, demonstration, and training.	9,600	6,900	9,600	4,531	6,400	−500	Reduction of 14 new training grants.
Technical assistance, services, and administration.	1,861	1,775	1,861	1,585	1,500	−275	Reduction of (1) $200,000 for public information activities and (2), net reduction of 3 positions.
Subtotal	26,461	19,675	26,461	19,220	18,450	−1,225	
Research and training (special foreign currency program).	250	----------	250	----------	----------	----------	
Total, AoA	26,711	19,675	26,711	19,220	18,450	−1,225	
SPECIAL INSTITUTIONS							
American Printing House for the Blind	1,264	1,264	1,264	1,264	1,225	39	Revision of the estimated cost per pupil for 19,840 pupils from $60 to $58.46.
National Technical Institute for the Deaf	6,296	6,296	6,296	6,296	2,615	3,681	Deferral of the funds for actual construction.

Summary of high and low dollar budgets, fiscal year 1968—Continued

Activity	As submitted by operating agency		As submitted by department to Budget Bureau		1968 President's budget	Difference between President's budget and low budget submitted by operating agencies	
	High (1)	Low (2)	High (3)	Low (4)	(5)	Item (6)	Explanation
Medical Secondary School for the Deaf:							
Salaries and expenses	$470	$470	$470	$470	$425	$45	Reduction in request for administrative planning.
Construction	1,030	1,030	1,030	1,030	275	−755	Deferral of actual construction.
Subtotal, model school	1,500	1,500	1,500	1,500	700	800	
Gallaudet College:							
Salaries and expenses	3,206	3,206	3,206	3,206	2,878	−160	Improvements of laboratory school.
Construction	3,097	3,097	3,097	3,097	2,196	−45	Assumption of 3 graduate school positions by grant funds.
						−73	Improvements in electronic data processing facility.
						−50	Improvements in maintenance service.
						−80	Planning for expansion of laboratory school.
						−585	Construction of library addition.
						−50	Construction of maintenance building.
						−186	Program of renovations.
Subtotal, Gallaudet College	6,303	6,303	6,303	6,303	5,074	−1,229	
Howard University:							
Salaries and expenses	15,852	15,852	[2] 16,069	[2] 16,069	15,300	+217	To remedy instructional deficiencies in school of dentistry reductions.
						−294	Improvements in liberal arts complex.
						−475	Physical plant renovations.
Construction	24,726	24,726	24,726	24,726	23,111	−400	Medical-dental library expansion.
						−200	Animal center, construction.
						−100	General library expansion.
						−915	Powerplant renovations.
Freedmen's Hospital	6,970	6,970	6,881	6,881	6,700	−270	Purchases of medical and surgical equipment.
Subtotal, Howard University	47,548	47,548	47,676	47,676	45,111	−2,437	
Total, special institutions	62,911	62,911	63,039	63,039	54,725	−8,186	

[1] Includes $1,000,000 for research grants sponsored by the Social Security Administration. This amount had been separately requested in a new proposed appropriation account of Social Security Administration. This amount is included here because the Budget Bureau disallowed the request for a separate appropriation account.

[2] Includes addition of $217,000 to remedy instructional deficiencies in school of dentistry.

ANNUAL PERCENTAGE BUDGET INCREASE

Mr. FLOOD. Leaving out the grants for construction and the regional medical program, the total increases are about $78 million or just under 8 percent. With a little prodding from Mr. Fogarty you made a pretty strong case for the proposition that programs such as yours require an annual increase of about 15 percent in funds just to maintain the same level of effectiveness. Well, in this budget where are you going with 8 percent?

Dr. SHANNON. Well, sir, your memory may be better than mine but that included the entrance of scientists we were training into the research field. That 15-percent figure was made up of three elements. The first was the increased cost of doing business, which we estimated would be 3.5 or 4 percent per year; the second element was the increased support for on-going scientific research as a result of the increased sophistication of techniques; this brought it to about 10 percent. Finally, we felt that about 5 percent additional would be required—until about 1975 when things started to turn over and the plant was established—for the entrance of new scientists.

Mr. FLOOD. Your memory is as good as mine. That is what you said.

Dr. SHANNON. I wanted to emphasize that I did include about 5 percent for the entrance of scientists we were training into the research field.

Mr. FLOOD. I know, but what happened? Have you fallen from grace or what?

Dr. SHANNON. I think the general answer to that is that the President and the Bureau of the Budget, in their wisdom, felt other programs could compete more effectively for new money than we could.

Mr. FLOOD. Mr. Natcher, will you proceed while I answer the rollcall.

RESTRICTED GROWTH OF FELLOWSHIP AND TRAINING PROGRAMS

Mr. NATCHER. Dr. Shannon, I notice there is no overall increase in the number of new fellowships you can support with this budget and there is actually a decrease in the number of training grants. How do you fit this in with all the talk about the need for more trained people in the field of medicine at this time?

Dr. SHANNON. All I can say is that we hope the present stringency of these funds will not hold too long because there are not sufficient funds for the plans we had for the next decade. I think the Bureau of the Budget has taken the attitude that for the moment, as they see the balance of the books, these programs must pause in their development.

APPROVED RESEARCH GRANTS COMPARED TO AVAILABLE FUNDS FOR 1966

Mr. NATCHER. Tell us in general what the situation is in regard to the number and dollar value of research grant applications that were approved during 1966 compared with available funds, and place a table in the record showing it by institutes.

Dr. SHANNON. Could we furnish that for the record?

Mr. NATCHER. Yes.

(The information follows:)

1966 research grant applications, approved, financed, and unfinanced

[Amounts in thousands]

Appropriation	Approved		Financed		Unfinanced	
	Number	Amount	Number	Amount	Number	Amount
Cancer	1,608	$59,745	1,453	$54,228	155	$5,517
Heart	2,197	82,351	2,171	81,710	26	641
Dental	425	13,428	339	11,263	86	2,165
Arthritis and metabolic diseases	3,087	82,804	2,796	75,204	291	7,600
Neurological diseases and blindness	1,874	59,710	1,676	54,495	198	5,215
Allergy and infectious diseases	1,626	45,348	1,348	38,271	278	7,077
General medical sciences	2,134	67,643	1,684	53,612	450	14,031
Child health and human development	1,065	34,136	1,065	34,136		
International research	129	384	129	384		
Environmental health sciences						
Total	14,145	445,549	12,661	403,303	1,484	42,246

Mr. NATCHER. In general give us the situation. What is it, Dr. Shannon?

Dr. SHANNON. There were shortages in research grant funds in all Institutes except two. In most of the Institutes there were substantial shortages.

Mr. NATCHER. What is the situation this year and what will it be in the new fiscal year if you get the amount that you are requesting, Dr. Shannon?

Dr. SHANNON. Viewed in terms of unpaid grant applications, we will have substantial backlogs of approved worthy applications in all Institutes, in all programs.

COMPARISION OF PHARMACOLOGY WORK AT NIH AND FOOD AND DRUG ADMINISTRATION

Mr. NATCHER. I notice in several places in your justification you made reference to work that you are doing in the field of pharmacology. What is the difference between what you do and what the Food and Drug Administration does and how are your activities coordinated?

Dr. SHANNON. To answer your last question first, we have liaison both at the top and at the bottom with the Food and Drug Administration. There is no block in the exchange of information.

As to the substance of the work, our porgrams, as distinct from the programs of the Food and Drug Administration, are aimed at the biological effects of drugs, whether there is a toxic or a therapeutic effect, and at an attempt to systematize this kind of information. For example, this effort underpins some of the work undertaken in the environmental health sciences. We know that certain chemicals at given levels produce intoxication. We do not know whether at low levels, over a substantial period of time, they will produce the same effect. Nevertheless, the laws of the land say that if any substance can be shown to produce a cancer in any animal form it cannot be used in medication. The theory is that these doses are cumulative and that the total dose is what is to be considered. This has never been demonstrated to be correct or incorrect but as we can measure smaller and smaller amounts of these materials, we place more and more substances

in jeopardy as to their use in the general economy, not because we know that they are hazardous but because we do not know that they are not hazardous.

It is beginning to be possible to classify therapeutic agents into very large groups, each group having characteristics different from other groups, which permits a more intelligent assessment of new agents and their properties rather than submitting them all to empiric tests. We are beginning to have an understanding of how these agents act in the cells and from this we are in a position to utilize therapeutic agents more intelligently.

The Food and Drug Administration is in the business of licensing or permitting to be sold in interstate commerce drugs and food, and their work relates to the specific products they have to deal with, and the amount of work they do in the general area is limited.

CARE OF ANIMALS FOR RESEARCH

Mr. FLOOD. All the Members, I believe, continue to receive many, many letters from people complaining about the cruel treatment of animals used in research. I suppose you know that?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Could you comment on that? A number of Members have asked me to ask you to comment on that.

Dr. SHANNON. Mr. Chairman, I was very glad to see passed, at the last session, legislation covering the transportation of animals. I was equally glad to see the responsibility for the care of animals recognized as an institutional responsibility. I was very glad that the legislation did not involve the setting up of a Federal bureaucracy to monitor the activities of literally thousands of laboratories spread across the Nation. I am convinced that with the number of scientists involved there are some abuses of animals. Scientists, as all humans, are not perfect. But I think this is unusual rather than usual and I think this occurs at a substantially minimal level and at a level that is probably unavoidable.

I think the main problem in the handling of animals is not in the experimental design or the use of animals in experimental situations, but rather in the resources available in schools and institutions and the facilities for the care of animals, particularly over a long period of time. As I testified before Senator Magnuson's committee and also Congressman Staggers' committee, the resources of this Nation are not adequate to carry the burden of the biomedical investigations that are going on.

Mr. FLOOD. What is that? What resources are not adequate?

Dr. SHANNON. The amount of biomedical research is beyond the animal resources of the Nation. From surveys that have been made, with our encouragement, it seems that 25 percent of the laboratory resources need extensive renovation and about 25 percent need replacement.

The executive branch proposed legislation to correct this in the form of preferential matching, for a limited period of time, for the construction of animal facilities—2 to 1 matching to permit the replacement of obsolete facilities. Unfortunately, this proposal came near the end of the session and was not enacted into law. Funds available

for construction are sharply curtailed, in relation to the authorization, so I do not think we will be able to do much to remedy this situation this year.

I am sorry, but I think that is the situation.

GEOGRAPHICAL DISTRIBUTION OF FELLOWSHIPS

Mr. FLOOD. I notice, in one of the Institutes justifications, a reference to getting a better geographical distribution of fellowships. Will you comment on that.

Dr. SHANNON. I would like to start off by saying that our programs in general are not expanding geographically last year or this year and, indeed, some of the research grants and training grants that were not renewed last year or will be renewed this year are from schools that desperately need support. But we feel that within the normal research program and the normal training program our objective must be excellence.

We feel other programs should be utilized to develop new capabilities in institutions where those capabilities do not exist. That is the primary thrust of the item for the Health Sciences Advancement Awards that Dr. Kennedy will speak to.

If you have a shortage of funds, you have to determine what is the best use for the funds you have. The program that has been developed by the Heart Institute, for example, for university-based heart institutes is in the geographic distribution business.

Mr. FLOOD. I would imagine geography is an important factor in other of your programs, too.

Dr. SHANNON. Yes, and I think that is shown in the regional medical programs.

Some of the newer therapies are so demanding of resources, they are so dependent on laboratories, that, in the absence of highly sophisticated skills, the application of these resources to patients is almost impossible. You might be interested to discuss with Dr. Endicott the setting up of a limited number of laboratories to develop a specialized therapy for choriocarcinoma. This will be a lifesaving device for about 5,000 women a year in the prime of their childbearing period. The therapy is so complicated that you have to have good resources which, for a national total of 5,000 patients, cannot be developed in every hospital, but it can be developed on a regional basis.

PROGRAMING-PLANNING-BUDGETING

Mr. FLOOD. You mention in your budget "Programing-planning-budgeting." What will you accomplish by that?

Dr. SHANNON. I will ask Mr. Seggel to answer that.

Mr. SEGGEL. We have about eight positions at this point.

Mr. FLOOD. What do you expect to accomplish by this?

Dr. SHANNON. We have analyzed our programs by Institute, by program, in a way that permits analysis of the program, the making of choices among alternatives, and planning for 5 years.

Mr. FLOOD. You have been doing that?

Dr. SHANNON. Yes, and we hope the Office of the Secretary will accept this analysis in the way the Department of Defense holds their

fundamental research and applied research on a level-of-effort type budgeting.

Mr. FLOOD. Oh, you had lunch with McNamara, did you?

Dr. SHANNON. No, sir. I know Mr. McNamara. We do not know if it will be accepted. Mr. Cardwell will comment on that.

Mr. FLOOD. Did you say eight positions? You have more than that budgeted for next year?

Mr. SEGGEL. Next year we have 15. Eight this year and 15 next year.

Mr. CARDWELL. This is an effort the Secretary would place very high priority on. He wants to install a systematic approach to planning.

NIH MANAGEMENT FUND

Mr. FLOOD. At several places you refer to the revised formula for distribution of the NIH management fund.

Mr. SEGGEL. This covers our central services, Mr. Flood, the clinical center, the research services, the provision and maintenance of utilities, the shops that maintain the plant, and so on, a whole variety of services in support of our research, but which we cannot allocate to each of the programs so under the authority given by this committee in 1958 we try to distribute these costs under a formula.

Mr. FLOOD. What is the revised formula?

Mr. SEGGEL. That is set forth in the justification statement.

Mr. FLOOD. I saw that.

Mr. SEGGEL. We revised it to make it a little more equitable. The GAO came around and discussed it with us and, as a result of this and a study we conducted, we tried to revise it in a way that will make it more equitable among the Institutes and budget activities.

Dr. SHANNON. I might say we do this periodically.

Mr. SEGGEL. It had not been done since 1961, and, as a consequence, we thought we should look at it again to get a better distribution.

REGIONAL MEDICAL PROGRAMS

Mr. FLOOD. What about your regional medical programs? I sat here and I listened to these declamations about regional medical programs and I heard the President's speech. I listened to you and everybody but the elevator operator about what we were going to do with the regional medical programs. What about the problems? What happened? It never got off the ground.

Dr. SHANNON. Mr. Flood, I am glad you asked me that question because I think I can clear up some of the general misunderstanding which might help Dr. Marston. I am not discouraged with the program but I think anticipation has been too high.

The act was passed in October 1965. Responsibility for the program was assigned to the National Institutes of Health in November and Dr. Marston came on duty in February 1966 with the establishment of the Division.

In the first place, there is confusion. The DeBakey report came out in December 1964 and we actually came up for a supplemental request for additional funds to implement the DeBakey report. The DeBakey

report had some 35 major recommendations that dealt with the Public Health Service, the——

Mr. FLOOD. We will have an opportunity to listen to him. He will be up here as an outside witness.

Dr. SHANNON. But the regional medical program concerned itself with only the first 3 recommendations. In the legislative process the regional medical programs, as proposed by the executive branch, underwent substantial changes. It was proposed for 5 years and was given 3 years. There was a substantial reduction in funds. Construction authority was removed. At the present time, the operation must be through a grant made to a regional body.

Mr. FLOOD. A regional body?

Dr. SHANNON. A regional council, I should say.

Mr. FLOOD. What is that?

Dr. SHANNON. This is a formally organized group that is recognized by the Surgeon General as representative of both the consumers, the educational community and medical community in a region.

In addition to these restrictions, a report is due about 18 months after the enactment of the legislation—that is on July 1 of this year. This program comes at a time when the universities are short of manpower, when there has been a curtailment of funds under the Health Professions Educational Assistance Act——

Mr. FLOOD. What year is that?

Dr. SHANNON. The present year, 1967—and when they are being asked by the Office of Economic Opportunity to undertake certain activities, and when the manpower shortage is somewhat aggravated by medicare. The lack of permanent authority has made the large universities hesitant to commit personnel to get the programs underway. It has been Dr. Marston's problem, which I think he has overcome in a masterly way, to convince these institutions that even though it is only a 3-year program at the present time which they can only mount on a pilot basis, that this will be made permanent, with such modifications of the basic legislation as is needed, sometime in the next Congress. On the basis of this assurance, most of the programs, particularly in the metropolitan areas, have gotten off the ground.

Mr. FLOOD. They have what?

Dr. SHANNON. They have gotten off the ground. Planning grants have already been approved for regions that include 82 percent of the population. Applications now being reviewed will bring that figure to 98 percent. I might point out that the bill provides that there not be a Federal program imposed from above but that the programs should emerge from the various forces within the regions. This involves what you did with the practitioners around Scranton.

Mr. FLOOD. Around where?

Dr. SHANNON. Wilkes-Barre. I am sorry.

Dr. Marston tells me that one of the reasons for the lack of activity in your area, sir, is that the application for a grant that came in from the group of institutions in Philadelphia, in its initial form, was so centered in the Philadelphia area as to be unacceptable to his staff or to the Council. It was sent back and after consultation with many people, including some from your area, it was resubmitted. This grant is about to be made. I do not blame you, Mr. Chairman, for being impatient. I think if you were to ask Dr. Marston while I am not

around, he would say that I am also very impatient with this program.

Mr. FLOOD. I really took the bait on this heart, cancer, and stroke business. What happened? Did the peach lose its bloom?

Dr. SHANNON. I do not think the peach has lost its bloom, I think the peach blossom has lost its petals. I would rather have a ripe peach than a peach blossom.

SMOKING AND HEALTH

Mr. FLOOD. With regard to smoking and health—Mr. Hull discussed this program with the Surgeon General and in the course of the discussion the activities of the Cancer Institute, Heart Institute, and the Division of Environmental Health Science were mentioned. Would you like to make some general comments on that?

Dr. SHANNON. Indeed I would, Mr. Chairman. I like to compare the relationship of smoking and health to simpler times when we were concerned with the relationship between poor sanitation and typhoid fever. By careful study it was possible to implicate the unsanitary circumstances with the emergence of the disease without, at the time, being able to identify the specific agent that produced the disease. But it was possible in subsequent years to define a simple cause-and-effect relationship, to isolate the organism responsible for the disease, and to control it.

I think smoking and health is in the stage today that typhoid fever and poor sanitation was in the early part of the century. There are now 52,000 deaths per year from lung cancer, and, if you can make a simple calculation—in 1965 there were 1.8 million deaths, and if you take a death rate of 50,000, in round figures, it meant that there was one chance in 36 of dying of cancer of the lung. Mr. Hull's comment about his family's involvement with tobacco for 100 years and having no experience of this sort is not surprising. It is not surprising because this disease was scarcely diagnosed until 1930 and did not become a common disease until the forties and fifties. I think that there is now no doubt in any professional's mind that the smoking of cigarettes is casually related to the production of cancer. Among people who develop lung cancer, if you compare smokers to nonsmokers the ratio is 9 to 1. If you consider this ratio and the 50,000 deaths a year and compare it with other medical phenomena, you realize what a terrible uproar we make about deaths from traffic accidents.

COST SHARING

Mr. FLOOD. Doctor, in your justifications you state in reference to one of your Institutes, "The newly authorized cost-sharing arrangements." What are the new arrangements, and how will they affect the percentage breakdown of cost between the Federal Government and the grantee?

Dr. SHANNON. We are encouraging our grantees, because of the limited funds available in the budget, to retain on their books the costs that are now being paid by their institutions in support of the research grant, be it salary or other object. In other words, we do not feel that we are in a position to absorb an additional portion of the cost of projects that are now substantially supported by the university.

This has particular relevance to the handling of grants held by

senior faculty who are on full-time salaries in the university.

Mr. FLOOD. You encourage them to do what?

Dr. SHANNON. To continue to pay what they have paid in the past.

Mr. FLOOD. This is right back where we started, then. What is the difference in the cost sharing now from what it was under the indirect cost limitation? We changed that to let you decide what the fair share is.

Dr. SHANNON. That was decided by the Department to be no less than 5 percent of the total cost. The result, in the operation of our programs, is not very different from the ceiling of 20 percent of the total cost of the grant for indirect costs.

It really amounts to the same thing. It has not materially helped the grantee institution, but there has been an increased tendency to put increasing amounts of faculty salaries on grants. At a time when the funds for research grants are not increasing substantially, we have pointed out to the institutions that we cannot bear increased costs on individual grants if we are to open any new areas of research whatsoever. We have said that it is in the best interest of science, generally, for the institutions to continue to bear whatever costs they are now bearing under the old pattern.

Mr. FLOOD. It is ring-around-the-rosie, right back where we started.

Dr. SHANNON. Back where we started; yes, sir.

DIRECTOR'S ADVISORY COMMITTEE

Mr. FLOOD. I have before me the Drug Research Reports for April 5, 1967. I see here a caption:

NIH Director's new advisory committee holds first operational meeting, but does not get down to specifics of what generally is considered its basic task: What form shall long-term plans for research take?

Under what rug is this one hidden? I never heard of this.

Dr. SHANNON. It is right on top of the table, sir. This is a committee that was recommended in the Woolridge committee report of some 3 years ago. The report pointed out that while the committee found no fault with program analysis and direction at the National Institutes of Health up until that time, it was their belief that the decisionmaking process should be made more visible and should make more direct use of external advisers. They felt that this could best be done by the official appointment of a committee to advise the Director of NIH. We accepted that as sound advice and recommended that such a committee be organized last spring, about a year ago.

At that time there was some doubt whether the Office of the Director of NIH could, indeed, have an advisory committee. The initial response was that there was no legal authority for such a committee. After we ironed that out, we were given permission to set up this advisory committee.

The new report is wrong in several respects.

Mr. FLOOD. Let me read you this, just to be sure, and you show us where they are wrong.

A two-day session deals primarily with general topics such as science manpower, avoids breakthrough predictions. Discussion of specific programs is limited to the proposed Fogarty memorial. Meetings are conducted against

background of both increasing concern by members of various advisory councils about fundamental scientific management philosophy, and questions posed by such figures as Assistant Budget Bureau Director Carey and Dr. Albert Sabine.

There is a combination—Carey and Sabine.

Dr. SHANNON. Mr. Chairman, I do not know what they are talking about. They were not at the meeting and, obviously, they do not know what went on. I would be very glad to give you a brief résumé of the committee, its membership and its task.

Mr. FLOOD. I wish you would, because we know nothing about it at all.

Dr. SHANNON. This was the second round of meetings rather than the first. They will meet again on June 13 and 14. They are doing precisely what we planned; namely, to take a look at some of our more important problems.

Mr. FLOOD. Suppose you prepare a statement on the committee for the record, then a paragraph or so as to what happened at the meetings.

Dr. SHANNON. We would be very glad to do that.

(The requested information follows:)

INFORMATION ON THE ADVISORY COMMITTEE TO THE DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH

ORIGIN OF THE COMMITTEE

The Advisory Committee to the Director, NIH, evolved from findings and recommendations by the "Wooldridge Committee" in its February 1965 report to the President, *Biomedical Science and Its Administration—A Study of the National Institutes of Health*. This distinguished Committee, established by the Office of Science and Technology at the request of the President, made these comments pertinent to the need for a high-level, nongovernmental group to advise on overall NIH operations:

"Principal Findings"—Page 1

"The most important organizational need of NIH is the strengthening of its capacity for long-range planning, for determining the optimum utilization of its funds, and for ensuring that its activities and policies have the continued understanding and approval of the scientific and lay public."

"Plans and Policies"—Page 13

"The Committee proposes the formation of a Policy and Planning Council, composed of prominent nongovernment scientists and laymen, to provide a high-level advisory service to the Director of NIH . . . (This Council) will assist the Director of NIH in his important over-all planning and policy-determining activities by bringing to bear on the issues involved the highest possible quality of informed and mature judgment. . . . The participation of such a nongovernment group in the major decisions of NIH will provide the needed assurance for the scientific community and the public that the Government is not, through NIH, exerting undesirable influence over the course of health-related science."

The concept of an Advisory Committee to the Director, NIH, was approved at Public Health Service and Departmental echelons; and in May 1966 the present Committee was established by the Director, NIH, using authorities delegated to him by the Surgeon General under Section 222 of the Public Health Service Act.

Functions

The Committee's advice will be sought on matters concerning overall direction and balance of NIH activities that are the appropriate concern of the Office of the Director. The Committee will be supported by *ad hoc* panels directed at the exploration of specific problems or issues.

In December 1965, the following functions were proposed and adopted for the Advisory Committee:

"The functions of this Committee will be:

(1) to consider matters relating to the broad scientific, technological, academic, managerial, and socio-economic setting in which the continuing develop-

ment of the biomedical sciences must take place and to advise the Director concerning their implications for policy, program development, resource allocation, and administration of the National Institutes of Health;

(2) to provide a framework for overall review and evaluation of specific or general aspects of NIH activities not encompassable within or appropriate for individual Institutes and Divisions;

(3) to reflect professional, scientific, academic, and managerial views and opinions concerning the conduct of NIH activities as a means of providing assurance that informed and mature judgment is brought to the broad process of decision which takes place in the Office of the Director of NIH."

Committee membership

The twelve Advisory Committee members appointed to date represent a broad spectrum of professional capabilities and interests pertinent to NIH programs, including higher education, the field of industrial research and development management, biology, medicine, behavioral sciences, physical sciences, and engineering. It is planned to appoint several additional members to the Committee when further experience indicates what advisory areas warrant further strengthening. Present membership of the Committee:

Dr. Douglas D. Bond, Professor of Psychiatry, University Hospitals, Cleveland, Ohio.
Dr. Philip P. Cohen, Professor and Chairman, Department of Physiological Chemistry, University of Wisconsin, Madison, Wis.
Dr. Maurice J. Hickey, Dean, School of Dentistry, University of Washington, Seattle, Wash.
Dr. Irving M. London, Professor and Chairman, Department of Medicine, Albert Einstein College of Medicine.
Dr. William D. McElroy, Chairman, Department of Biology, Johns Hopkins University.
Mr. V. G. Nielsen, Secretary and Trustee, Aerospace Corp., El Segundo, Calif.
Dr. G. Franklin Edwards, Professor of Sociology, Department of Sociology and Anthropology, Howard University.
Dr. Caryl P. Haskins, President, Carnegie Institution of Washington.
Dr. Henry W. Riecken, Vice President, Social Science Research Council.
Dr. Wendell M. Stanley, Director, Virus Laboratory, University of California, Berkeley, Calif.
Dr. Jerome B. Weisner, Provost, Massachusetts Institute of Technology.
Dr. Barnes Woodhall, Vice Provost, Duke University Medical Center.

Committee activities

The Advisory Committee to the Director, NIH, has held three meetings since its establishment: the first on November 18, 1966, and again on January 30–31 and April 3–4, 1967. A fourth meeting is scheduled for June 14–15.

Typically, the first morning of these meetings is devoted to items of general interest, to keep the Committee members informed on recent developments affecting NIH programs. In addition, at each session, one or more selected program topics (of major concern to the Office of the Director) are reviewed and discussed in detail.

A series of panels is being set up to consider areas of concern to NIH, broadly. It is envisioned that these panels will be made up of Committee members and other consultants appropriate to the subject matter. The first two of these panels will be concerned with the role and program possibilities of NIH in (respectively) bio-engineering and the behavioral sciences.

Mr. FLOOD. Mr. Laird.

HEW BUDGET PRIORITIES

Mr. LAIRD. Thank you, Mr. Chairman.

Dr. Shannon, this morning in our discussion, Mr. Cardwell indicated that priorities were established in the budget submissions that were made by the NIH and by the other bureaus and divisions of the Department of Health, Education, and Welfare. We have been having hearings here for several weeks, but the first knowledge that I had that a priority arrangement was arrived at by the various agencies

was the statement that Mr. Cardwell made this morning. Just how does that work?

Dr. SHANNON. Maybe Mr. Cardwell will correct me——

Mr. LAIRD. Maybe I should address it to him.

Mr. CARDWELL. I will be glad to attempt to answer. As I tried to say this morning, in recognition that this was going to be a tight budget this year, and in recognition of the pressures of Vietnam and the question of inflation, we decided that we would develop two budget levels throughout the Department for presentation to the Bureau of the Budget.

We made a proposal to the Director of the Bureau of the Budget that we would do so. In effect, we set up what we called a high budget and a low budget for each major agency and within the National Institutes of Health, for each major activity.

The first budget in the aggregate was within a total ceiling of about $13.5 billion which the Bureau of the Budget set for the submission for our fall budget.

Mr. LAIRD. That was your overall ceiling; and that was your high budget?

Mr. CARDWELL. This was the Department's low budget.

Mr. LAIRD. I want to get this straight, because this is very important.

Mr. CARDWELL. Then we sent to the Bureau of the Budget in the fall a series of proposals that in the aggregate amounted to $13.5 billion. We also sent a series of additional proposals which, when added to the $13.5 billion, added up to $15.8 billion.

Mr. FLOOD. Was that a class B budget, then?

Mr. CARDWELL. In effect, it was very similiar to the old A and B budgets. The proposal was that we wanted the Bureau of the Budget and, if necessary and appropriate, the President, to examine those program items that were in the higher budget because the Secretary felt they were important. They were of high priority, but they were of lower priority than the items that were in the $13.5-billion budget.

Mr. LAIRD. In whose judgment?

Mr. CARDWELL. In the judgment of the Secretary.

Mr. LAIRD. I think for the record we want to get the priorities that were established in each division, each institute, each bureau, each working agency of the Department of Health, Education, and Welfare.

Mr. FLOOD. And each activity, if possible, of the NIH.

Mr. LAIRD. Yes. I will get into that a little later on. I want it now for the Department.

Mr. CARDWELL. Let me identify the kind of information we have available that we could furnish for the record.

For each major operating agency we can identify for you the high budget and the low budget and the items in the two budgets that were different. We can list those program items. We can also list for you the items of lower priority that were not included in the President's final budget, and those items that were proposed to the Secretary, considered by the Secretary, and submitted, which did not end up in the final budget.

Mr. LAIRD. Of course, the final budget is $13.3 billion.

Mr. CARDWELL. Right.

Mr. LAIRD. So you are talking about $200 million worth of lower priority items.

Mr. CARDWELL. No, I am talking about $2.5 billion worth of items.

Mr. LAIRD. You are talking between the high and the low; but you are not talking between the low and the final budget submission. The low budget is $13.5 billion, and the budget that you have before this committee now is $13.3 billion. So, you are talking about $200 million there. Let us get into the differences now between the $13.5 billion and the $15.8 billion. Let us discuss that now.

Mr. CARDWELL. We can furnish that by agency and within the National Institutes of Health by activity. We cannot take it below activity because it was not requested nor was it submitted below activity.

Mr. LAIRD. You asked for priorities, I would assume, between the high and low budgets, though.

Mr. CARDWELL. No, we did not.

Mr. LAIRD. You have no priorities, no information given to you on priorities? I would think that would be the first thing you would ask for.

Mr. CARDWELL. The line drawn on priorities was: Give us those items that you believe to be of such high priority that they should be fitted within the so-called low budget. They were proposed to us as the highest priority items. The items that made up the difference between the $13.5 billion and the $15.8 billion were identified as being of lower priority, but as a block. In other words, there were two blocks of priorities. The highest priority items went in the so-called low budget. The lower priority items went in the so-called high budget.

PRIORITIES IN OFFICE OF EDUCATION BUDGET

Mr. LAIRD. I understand you have no priority information at all submitted to you by any agency, such as the Office of Education, on priorities between the $13.5 and the $15.8 billion? Did not the Office of Education indicate to you some of the highest priority items that were left out of the budget and, if you were to increase the budget by, say, $200 million, what the highest priority items would be?

Mr. CARDWELL. In this way: In effect, the answer to that is yes.

Mr. LAIRD. That's fine. Let us take the Office of Education and then we will get back to the NIH. I want to know, for the Office of Education, what the difference was between their low and high budget.

Mr. CARDWELL. By item?

Mr. LAIRD. By item. Then I want to know their priorities. I want to find out where you made a change and where you followed the Office of Education's priorities.

Mr. CARDWELL. The Office of Education's priorities would have been established in an evolutionary way. If the Bureau of the Budget proposed to deny an item that was in the low budget, the Commissioner of Education was asked to evaluate the effect of that proposal on his total program. He would indicate to us those items that he wanted appealed. The Secretary reviewed them from the same point of view. In this way he established priorities. We appealed the highest priority items. We stepped back and accepted the Bureau of the Budget allowance on lower priority items.

Mr. LAIRD. I am using the Office of Education budget as an example just for information, because you have overall responsibility.

Mr. CARDWELL. Correct.

Mr. LAIRD. How many of the items not in the low budget as originally submitted were deleted for items given a lower priority by the Office of Education.

Mr. CARDWELL. Yes.

Mr. LAIRD. How many were there?

Mr. CARDWELL. I do not know that there were any.

Mr. LAIRD. You did not override the Office of Education in the establishment of any priority item in the budget? You, the Bureau of the Budget, or the White House?

Mr. CARDWELL. I would like to check the record to be certain of the answer.

Mr. LAIRD. I would like to have a listing of all items on which a bureau or agency in the Department was overridden as far as the priority of an item was concerned.

Mr. FLOOD. By the Bureau of the Budget?

Mr. LAIRD. Or by the Secretary for inclusion. I am talking about inclusion now. Do you follow me?

Mr. CARDWELL. Yes, I do. Let me put your question as I understand it: If an item had been identified in the so-called high budget and later showed up in the final budget, you want a listing of such items, because that would indicate that we made that a higher priority, "we" being the Secretary or the Bureau of the Budget or the administration, than the operating agency making the proposal. Is that correct?

Mr. LAIRD. That is correct. You indicated there were not any.

Mr. CARDWELL. I am not certain that there are any. I would not think that there were any. There may be some isolated situations.

ARTIFICIAL HEART AS AN EXAMPLE OF PROCEDURE FOR ESTABLISHING PRIORITIES

For example, I can recall that the artificial heart budget came under special examination because the Congress took action which affected the 1968 level of that program after these two budget levels had been established. That action occurred after the original submission by the National Institutes of Health and by the Surgeon General. So, we did perhaps make some shifts, recognizing the fact that the Congress added money in that program.

Mr. LAIRD. Taking that as an example, I would like that fully explained. I do not quite follow you. You mean in our budget markup in October we made some shifts that required you to make changes?

Mr. CARDWELL. Yes.

Mr. LAIRD. Tell me what those were.

Mr. CARDWELL. I do not have the figures at hand. I just remember the item.

Mr. FLOOD. Since we have the NIH here, why don't we make a guinea pig out of this program? This is a good idea. We can find out what happened.

Mr. LAIRD. Take the artificial heart as an example.

Dr. SHANNON. I cannot give you the historical development of this item except in very general terms. I think we can reconstruct it from our notes.

Mr. LAIRD. Mr. Cardwell brought this up as an example and, as long as this is the one that he pointed to, let us take this as a guinea pig, as the chairman suggests.

Dr. SHANNON. My recollection of that item is that we had in the 1967 budget, as a result of the Congress action, a sum slightly in excess of $15 million.

Mr. CARDWELL. That is right. At the time the original budgets were put together, the first submission, there was about $5.7 million put in the high priority budget for this purpose. The Congress added $15 million. So, we had to go back and reevaluate the impact of that on the 1968 budget, and the original submissions that were made did not take that into consideration. They could not take it into consideration.

Mr. LAIRD. Who did the reevaluation, the Heart Institute or some accountant over in the Bureau of the Budget? Who did this reevaluation?

Mr. CARDWELL. The National Institutes of Health, of course, was the program involved, and the Office of the Secretary's staff, including our staff, would arrange for this to take place.

Mr. LAIRD. This is something that was in the high budget. You moved it down into the low budget?

Mr. CARDWELL. I do not recall specifically how it fell into the two budgets, if at all.

Mr. LAIRD. Do you have the low and the high budget with you?

Dr. SHANNON. We do not have that. We would have to furnish it for the record. Although the 1967 figure was substantially higher, as it came out of the Congress, than was anticipated in the original President's budget, it was our judgment that, with the change of Institute Directors and the change in leadership of the program, it probably ought to be continued roughly at the same level in 1968 as in 1967.

I think our discussions with the Bureau of the Budget involved their willingness to accept a substantially higher figure in 1968 than we had proposed. I can reconstruct this.

Mr. LAIRD. For the record, could we have this? This is an example which Mr. Cardwell uses as one of the items which has been moved around.

Mr. CARDWELL. The congressional action occured after the original submission. That is the reason I identified it.

Mr. LAIRD. Let us make this clear. We took final action on the artificial heart program about the first of October.

What will the expenditure rate be in the artificial heart program in fiscal year 1967?

Dr. SHANNON. The expenditure will be substantially below the authorization.

Mr. LAIRD. I am talking about the expenditure, because this governs what we do in 1968.

Dr. SHANNON. This will be below $15 million. I do not know precisely, but I think Dr. Frederickson may have a better figure when he comes before you. It may well be that we can reconstruct that history before you meet with Dr. Frederickson for the Heart Institute.

I would emphasize taht a good deal of the decisionmaking on specific items, such as this, were the result of verbal discussions, and it may well be that it will be difficult for us to find in our records spe-

cific decisions that were made, other than our own internal memorandums.

Mr. FLOOD. We haven't got much of a guinea pig.

Dr. SHANNON. You must realize that we are rather distant from the Bureau of the Budget. They operate with the Department. The figure comes to us and the usual response is, if we find the figure unsatisfactory in terms of what we feel the program should be——

Mr. LAIRD. You are really not the best witness in this area.

Dr. SHANNON. No, sir. I think the Department is the best witness.

Mr. LAIRD. We have to go to the Department, because this evidently is a departmental decision and not an NIH decision in this case.

Mr. CARDWELL. The artificial heart decision?

Mr. LAIRD. Yes.

Mr. CARDWELL. No, I do not think so.

Your question to me was, could any changes have occurred between these two levels, and I said I did not think such changes occurred but they may have. I thought of one instance in which it might have occurred. I am not sure whether it did or not.

Mr. LAIRD. You brought up the subject. I did not bring it up. You used this as an example, right?

Mr. CARDWELL. Right.

Mr. LAIRD. I am just trying to figure out what happened in this example.

Mr. CARDWELL. I would like to check the record. I cannot tell you from memory what happened, but I think the record will show.

Mr. LAIRD. Do you know what happened, Mr. Kelly?

FORMULATION OF BUDGET ESTIMATE

Mr. KELLY. I would like to comment on the problem. I think the discussion which you and Mr. Cardwell have had has been illuminating and indicates a set of circumstances that would lead you to believe that each stage of this process is an arm's-length stage that is definitive in and of itself.

We gave you some tables saying what the operating agency asked for, what the Department asked for, and what the Budget Bureau allowed.

Mr. LAIRD. I have those tables before me. From this discussion I guess they are not very complete because there must have been two or three other budgets that you have left out.

Mr. KELLY. That is right. During this entire process—this process flows together—there are continuing communications between the operating agencies, the Secretary, and the Budget Bureau, with changes occurring.

The point Mr. Cardwell was trying to make on the artificial heart is that when we initially ask for budgetary data——

Mr. LAIRD. He was trying to use the artificial heart as an example because he thought he could use our committee as a basis for doing this. I do not think this committee has anything to do with the 1968 budget until we act on it.

Mr. KELLY. No. It is a wonderful example of the basic problem of constructing a budget and reconstructing what occurred.

The National Institutes of Health and the Public Health Service commenced the development of the 1968 budget well before the Congress acted on 1967.

Mr. FLOOD. About what month?

Mr. KELLY. Maybe 3 months before. Maybe they started in February and started presenting us data in April and in May. So, in order to do that, we asked them to start with the assumption that the Congress approved the 1967 budget unchanged. Therefore, this becomes their base.

Using that as a base, they said that they would be in a position to spend $5 million in 1968 within the constraints that were established for the development of the artificial heart; but before we had reached the point of formalizing and finalizing this budget, the Congress has decided that the 1967 program should be a larger program than had originally been predicted for 1967. This necessarily made us change 1968 to recognize this change in base.

So, during this period in which these data flowed back and forth, the 1968 budget had to be updated and changed to fit changing circumstances. Part of those changing circumstances are the actions of the Congress. Part of them are our own actions, that we moved either more quickly or more slowly than we anticipated we would.

In essence, the total amount of the budget for the National Institutes of Health is a decision that is made by the President on the advice of the Bureau of the Budget and on the advice of the Secretary. The distribution of that total budget among the various items and kinds of programs that are conducted is primarily determined by the Surgeon General and the Director of the National Institutes of Health in collaboration with their staffs because they, within those constraints and within those limits, are more capable of developing the kind of a program would best fulfill the roles and responsibilities of their agencies.

You can reconstruct any one of these items.

Mr. LAIRD. That is why it will be interesting to see the priorities established between all items in the low and the high budget. It is nice to have this chart, but the priorities are the important thing. You understand that.

Mr. FLOOD. And who determined them.

Mr. LAIRD. I think I had better drop that, because I am not getting very far and no one has much material available today. I hope you can supply it for the record.

(The information requested appears on pp. 29–40.)

REGIONAL MEDICAL PROGRAMS

Mr. LAIRD. We are going to get into a discussion of the regional medical programs a little later on, Dr. Shannon, when the item comes up. But since the National Institutes of Health has overall responsibility in this area, and while you are here I would like to ask you whether you think this program has gotten off the ground.

Dr. SHANNON. Within the legislative guidelines given us to operate the program, I think, indeed, it has. I think the guidelines themselves impose restrictions which tend to slow program development but, be that as it may, these are the legislative authorities we have, and with

a complex program such as this, I believe it is moving as fast, in general, as one could expect.

In certain areas it is moving faster than we had hoped. In others, I think it is substantially slower. We anticipated from the beginning that our hardest nut would be the large metropolitan areas, and this is, indeed, turning out to be the case. We felt in the beginning that our simplest problem would be in States with a single university that already has some network arrangement of a partially regionalized basis on which it can build. This has, in fact, turned out to be the case.

Our problem areas are the metropolitan areas, particularly where there are very elaborate, very sophisticated, very excellent centers that have been isolated, by the nature of their operations, from the surrounding community. Such centers now find that the implementation of this program demands quite different social attitudes in terms of the responsibility of the university toward the community which it will now serve.

This, coming at a time of uncertainty as to the future of certain other elements of their program supported by the Federal Government, and in the face of personnel shortages, has caused serious problems.

I am never satisfied, but I think the leadership of the program is extraordinarily good. I think the ability of the leadership to interact with the universities and the regional people, including the consumer as well as the university and State agencies——

LEADERSHIP IN REGIONAL MEDICAL PROGRAM

Mr. FLOOD. What leadership? Where is the leadership?

Dr. SHANNON. It comes from different places. It may be a State university, so designated by the Governor. It may be leadership that comes from a university group that elects to serve as the catalyst to form a group which then becomes the applicant. It may be a State medical society that decides that it has such a stake in the State that they should exercise leadership in bringing the group together. Or it may be the Department of Health.

Mr. FLOOD. You will have everybody at each other's throats.

Mr. LAIRD. This is the point I want to develop. I just do not think there is any real leadership in this program, and the problem that bothers me the most has to do with the lack of leadership and planning from the top down. This kind of program cannot be planned from the bottom up. It has to be planned from the top down. It is a little bit different from the kind of research that the Institutes have been carrying on.

I met with one of the men in charge of our program in Wisconsin, and I was shocked to learn that they were soliciting ideas and applications from all over the State. I can go out and get you all kinds of applications, if that is what you want, but that is not what should be done in this program. There should be a State plan, and there should be centers established around the State in various areas. We should make the best medical service available in the State available to all the people in the State.

In a thumbnail sketch, that is what I thought it was all about.

Dr. SHANNON. You are in large part right, Mr. Laird, but I would say the guidelines are very well and clearly delineated. Our legislative authority does not permit us to conduct direct operations either on a demonstration or direct basis, but limits our ability to operate through any mechanism other than through a regional planning group, that is recognized as such by the Surgeon General, for the given area.

Mr. FLOOD. This regional thing is created. Here is a vacuum. There is an old adage in infantry tactics, "occupy the high ground." Whoever occupies the high ground will command the field. Whoever first occupies the high ground here commands the field, whether they are the best qualified to lead or not.

Dr. SHANNON. As best I can judge, the high ground will have been occupied by groups that are satisfactory to the regional medical program and to the Surgeon General in 90 percent of the areas within the United States by next October. This does not mean that everybody who applies will be accepted as leaders. It does not mean that every grant application which is requested will be paid.

One of the problems was that very few of the initial grant applications were suitable either from the standpoint of how they proposed to plan, the region they proposed to encompass, or the relationships that the institutions in the group proposed to have with each other.

Be that as it may, when one attempts to move with a Federal operation into what, heretofore, has been a wholly private enterprise—namely, the practice of medicine—I think one had better move quite slowly, although positively and firmly, and within well-stated guidelines. Otherwise, we lose what we have and we gain nothing.

This may make you, sir, and me, impatient at the progress, but I think it is the price we have to pay. As I said this morning, I believe the petals are off the peach blossom; we are now in a position to reap the harvest of the ripe peach.

COMMITTEE REPORT LANGUAGE ON REGIONAL MEDICAL PROGRAMS

Mr. LAIRD. Last year in our committee report we discussed this at some length, Dr. Shannon. We said in that report, and I quote:

> There is widespread interest in the Regional Medical Programs in virtually every part of the country and in many regions considerable progress has already been made in the development of local plans. The Division's concientious efforts to keep representatives of interested groups informed of the latest administrative developments and to answer the hundreds of inquiries regarding the program that began to come in even before the authorizing legislation was finally enacted have been most commendable. The Committee was also pleased to learn that the development of a diversity of approaches—in accordance with regional needs, resources, and initiatives—will be encouraged by the staff of the Division. In this connection the Committee is disturbed to note that there is a tendency on the part of many people to think of the centers for these regional programs only in terms of the large medical complexes directly connected with a medical school. It will be expected that careful consideration also be given to such medical centers as the Marshfield Clinic about which this Committee has heard so much. The Committee will follow this new program with great interest and we expect to be kept informed about new program developments during the coming year.

REGIONAL MEDICAL PROGRAM IN WISCONSIN

I discussed this matter with the director of the program in our State, and I was surprised to learn that you could not initiate a program yourself in the State group; that they had to have an application

submitted. I thought the planning money was made available so the State or regional group could use this planning money themselves to plan. I had advised against filing applications on an individual basis to anyone who wrote me. I had informed them that a planning grant had been made in this region and that the planning committee would devise a statewide plan. This would not follow the same procedure that the various Institutes out at NIH follow as far as the research grant program is concerned.

Maybe I gave them the wrong advice.

Dr. SHANNON. Sir, I think your advice was substantially correct. Dr. Marston is fully prepared to give you the details as to what is going on in that State.

Mr. LAIRD. I will get into that in some detail with Dr. Marston when he appears before us, but it just seems to me that instead of doing this planning on a regional basis, we are trying to do it on a piecemeal approach. The applications in my State were very small and limited in scope. They were good, fine applications for good programs, but not suggestive of a regional, comprehensive approach.

An example was a telephone program carried on at the University of Wisconsin. You could dial a certain number and get an answer to a specific problem. It is good for the local doctors. This program has been going on at the University of Wisconsin for 18 months. Bell Laboratories and others are interested in it and it is a fine thing. I am not against it at all. It gives rapid answers to doctors who are out practicing in the field. This is good.

But that is not what I thought the regional program was all about.

Dr. SHANNON. Mr. Laird, I would defer to Dr. Marston when he appears to discuss the situation as he sees it, statewide, in Wisconsin.

Mr. LAIRD. I do not want to be too provincial about it.

Mr. FLOOD. You are not being provincial. You are no more provincial than I am. My concern, Doctor, is very much along this line. I had the same concept Mr. Laird has when we started out. I sat up there and heard the President read this speech and I got all hopped up. About a month later when I got to the hearings I found that is not what he said at all. An entirely different concept came out down here than you and I heard on the floor in that Presidential message that night.

EASTERN PENNSYLVANIA REGION

All right, I start all over again. I take off the mustache and I am another fellow now. Then I start with the Philadelphia people. I get hold of Dr. Marston. My idea was to set up the major center in this tremendous medical complex in Philadelphia which is beyond my understanding—hospitals, universities, clinics, for 50 square miles.

This is all right. In Defense we call it the mother hen concept, you remember. We will set up a plan. This is the prime contractor to make an aircraft. Then around it you set up a lot of satellites. This is the mother hen concept. There is mama, the big prime contractor. Around the mother hen are all these little chicks, and the sub-sub-subcontractors, all over the country. This is OK. I told these people this is all right. I know how this works.

So, we started to set it up. But now I am afraid I am getting jockied into a bad position if and when they go ahead with this mother hen

idea in Philadelphia, which I hope they are now finally going to do. The presidents or the deans of the medical colleges will come to me with their ideas on what ought to be done. Two already have. These fellows were not working together at this time. One did not know the other had called.

I think this is what Mr. Laird is talking about. This regional idea is sound, but I do not like the idea of these medical people in Philadelphia putting this thing all together by themselves and then calling me on the phone some day finally, if I live long enough, and presenting me with a fait accompli.

My idea was then to set up in my congressional district of three counties, a subregion. This is the region. Then I wanted a subregion set up of these three counties. I talked to the medical association presidents and nearly fell off the chair when every president of every medical association, every administrator of a dozen hospitals, everybody from three counties went to four meetings.

I am afraid that the Philadelphia people are not going out into the satellites and are not going to ask my medical associations, not ask my hospital administrators, not ask anybody outside Philadelphia anything. This is wrong. I expect them, before they do anything in Philadelphia, to go out into the provinces and find out what the satellites think, or want, or feel, or believe, because they are for it.

This was the original concept. I do not see why it cannot be done. I want you to talk to the people in the subregion before you create the region.

Dr. SHANNON. All I can say, sir, is that it is Dr. Marston's group's responsibility——

Mr. FLOOD. And he is doing a good job.

Dr. SHANNON (continuing). To see that the people in Philadelphia do not stay in Philadelphia; that they do create these associations, because this is what the ball game is all about.

Mr. FLOOD. I have no complaint against Dr. Marston. He has been standing by for 2 or 3 months waiting for somebody to ask him to come in.

Dr. SHANNON. You may be assured, sir, that a plan will not be approved for Philadelphia that does not encompass most of the elements you have talked about.

Mr. FLOOD. Or any place else?

Dr. SHANNON. Or any place else.

Mr. FLOOD. Philadelphia is just exhibit A. You are not going to establish these regions pro forma out of whole cloth without consulting the medical associations and the hospitals and the professionals that will be related to that region.

Dr. SHANNON. I agree, sir.

Mr. FLOOD. Just take a look around this table. Outside of Mr. Casey, who is a city boy, the rest of us are from the provinces.

DEEMPHASIS OF TRAINING IN THE BUDGET

Mr. LAIRD. Mr. Chairman, I will get off that subject and get on another one.

Dr. Shannon, in the overall budget for the National Institutes of Health this year there is a substantial decrease in program level so

far as the training of individuals is concerned. We have had a steady progression in this area from 1958 through the 1967 budget. This progression for training personnel is materially changed in this budget, is that not true?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. The research level is not materially changed in the budget submitted to this committee. There is not the same progression but there is not a decline as in the training programs. The number of research projects, of course, shows not as great as increase as we had in 1967, but there is an increase of 422 as far as the regular programs are concerned. Is that correct?

Dr. SHANNON. Yes, sir. In the training program, you will notice there is an increase in the dollar level. It moves from roughly $134.5 million to $139.6 million.

Mr. LAIRD. I see a reduction of 31 in the number of training grants.

Dr. SHANNON. There have been minor changes in training stipends. There have been substantial increases in salaries and staff. The result is that, with the increased cost of training an individual, it costs more now than it did a year ago and this adjustment makes up for a 2-or 3-year period when no changes were made. The option we had was either to maintain the quality of a lesser number of training programs or decrease the competence of all, and we chose to reduce the number and maintain the quality. So there will be 31 less training grants this year than last.

Mr. LAIRD. The problem we have been confronted with on this committee from time to time is that we have been making money available for research more rapidly than personnel and facilities. And when we see the personnel training programs cut back and the research facilities programs reduced, we wonder what that means. Do you feel we have reached the level of training and the level of facilities that is necessary to maintain our research work in accordance with the budget submitted here? We would like to have your best professional judgment on this. We have talked about this for some time and when I look at the increase in general research support and in the overall research program and I see a curtailment in personnel training and a curtailment in facilities, I just wonder if these three things should not be better balanced?

Dr. SHANNON. Mr. Laird, it was our recommendation to the Department, concurred in by the Bureau of the Budget, that training should be at a substantially higher level than this budget shows. We had the choice to make, under a lower ceiling, either to reduce research grants or to reduce training in order to encompass both activities under the ceiling. It was our feeling that, if this was a short period of reduced support, we should ride through a period of scarcity by curtailing the training of new scientists. Among research, fellowships, and training, the sharpest reduction we had to make was in training—that was by about $11 million. But you must realize that for research grants the Department proposed substantially more than we received and we in turn proposed substantially more than the Department was willing to submit to the Bureau of the Budget. So the budget before you reflects, to my mind, not what is desirable but, within a given ceiling, the best distribution that we can make.

COST TO RESTORE TRAINING GRANTS TO LAST YEAR'S LEVEL

Mr. LAIRD. How much would those 31 training grants cost?

Dr. SHANNON. In round figures, $50,000 or $60,000 apiece, on the average.

Mr. LAIRD. How much would it be for each Institute, the total amount involved here?

Dr. SHANNON. It would be a cutback of three or four training grants.

Mr. LAIRD. Insert that in the record.

Dr. SHANNON. Yes. The average training grant is in the range of $50,000.

Mr. LAIRD. For the record, if we could have it by Institute.

Dr. SHANNON. Yes, sir.

(The information follows:)

The decrease of 31 grants in 1968 is the net result of increases of 39 grants in six institutes and decreases of 70 grants in four institutes. If these 31 grants were distributed among the four institutes with decreases, in proportion to the amount of the decrease, the distribution, and the cost of the grants would appear as follows:

Organization	Number	Estimated cost
National Heart Institute	7	$311,654
National Institute of Neurological Diseases and Blindness	11	337,205
National Institute of Allergy and Infectious Diseases	5	255,945
National Institute of General Medical Sciences	8	532,096
Total	31	1,436,900

The decrease in the number of Training grants that will be supported in 1968 is due primarily to increases in the average cost of on-going training programs. These cost increases are the result of program expansion in established training programs, stipend and allowance increases, and general cost of living increases.

Dr. SHANNON. I am not happy to see training cut back but it was not a question of whether we cut here or there but how much we cut in both places.

THE JOHN E. FOGARTY INTERNATIONAL CENTER

Mr. LAIRD. Dr. Shannon, on the 18th of January 1967, we had on the floor of the House of Representatives eulogies to the late chairman of this committee, the Honorable John E. Fogarty, of Rhode Island. At that time I suggested on the floor of the House the establishment by this Congress of the John E. Fogarty International Center for Advanced Study in the Health Sciences. I would like at this point to insert the statement in the record which I made, with the chairman's permission.

Mr. FLOOD. Without objection it is so ordered.

(The statement follows:)

Mr. LAIRD. Mr. Speaker, JOHN FOGARTY's deep and devoted interest in international health and his conviction that through international exchange in the health sciences, a significant contribution could be made, not only to the solution of health problems but also to the advancement of world peace is, perhaps, best epitimized in his remarks before a panel on Health for Peace during the meeting of our Citizens Committee for the World Health Organization held in Washington in September 1963. The final paragraph of JOHN's remarks is of particular significance and I should like to quote it here:

"In concluding my remarks I would like to set forth an idea and a view which I feel to be of the greatest importance and significance. Instead of a curtailment of the programs and activities of the United States in the field of international health research. I should like to see a plan to bring into being at Bethesda a great international center for research in biology and medicine dedicated to international cooperation and collaboration in the interests of the health of mankind as so boldly envisaged by the President. The center would encompass conference facilities, laboratory and study space, and living quarters to permit the assembly for discussion, study, and research of the outstanding health scientists of the world. I visualize this center associated with the great facilities of the National Institutes of Health and the National Library of Medicine as representing the visible and tangible embodiment of this Nation's devotion to the use of science for peaceful purposes and the good of mankind."

I can think of no more fitting and lasting tribute to this great humanitarian, than the establishment by this Congress of such a center—the John E. Fogarty Internation Center for Advanced Study in the Health Sciences. I have talked with most of the members of our committee about this and they have all been enthusiastic in their support. I am sure that support will be unanimous, both in our committee and in the entire Congress. Not only will such an institution be a living embodiment of the spirit and aspirations of JOHN FOGARTY, but it will serve a needed and valuable role in securing the progress of science in the cause of the well being of all mankind.

REQUEST TO THE DEPARTMENT FOR INFORMATION AND PLANS

Mr. LAIRD. On the 24th of March the staff assistant to this committee addressed a letter to the Department of Health, Education, and Welfare informing the Department that we would like to have as much background material as we possibly could get, I also had discussed the center and requested that NIH and the Department of Health, Education, and Welfare develop material for submission to this committee at the time of our budget hearings on the 1968 budget. This was about 2 months ago.

I would like to include at this point in the record the letter to the Department and also the reply signed by Mr. James B. Cardwell, Deputy Assistant Secretary, Budget, of the Department of Health, Education, and Welfare, a rather unsatisfactory reply to say the least to be received by a congressional committee.

(The letters referred to follow:)

MARCH 24, 1967.

Mr. JAMES F. KELLY,
Assistant Secretary, Comptroller, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. KELLY: Both Mr. Flood and Mr. Laird have asked me whether any materials have been furnished by HEW that would provide a basis for a Committee determination with regard to financing the International Center for Advanced Study in the Health Sciences which the President mentioned in his Message on Education and Health.

As you know, Mr. Laird has proposed the establishment of such a Center as a memorial to John E. Fogarty. Mr. Laird has informed Mr. Flood of his desire to discuss this proposal with the NIH representatives when they are before the Subcommittee in the course of the current appropriation hearings.

I should like very much to provide Mr. Flood and the other Committee Members with as much factual information about the plans for the International Center as I can as a basis for this discussion.

Would you please arrange to have prepared and submitted to the Subcommittee by April 3, such plans and information as you consider appropriate to this purpose.

Sincerely yours,

ROBERT MOYER,
Staff Assistant, Labor-HEW Subcommittee.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., April 3, 1967.

Mr. ROBERT MOYER,
Staff Assistant,
Labor-HEW Subcommittee,
House of Representatives,
Washington, D.C.

DEAR MR. MOYER: This is in reply to your letter of March 24. The Public Health Service has submitted a proposal for the establishment and financing in 1968 of an International Center for Advanced Study in the Health Sciences.

The proposal has been reviewed and approved by the Department. It was delivered to the Bureau of the Budget this morning.

Since it has not, as yet, been reviewed by the Bureau of the Budget, we are not at this time able to furnish it to the Committee in time for the Surgeon General's testimony. We have been advised, however, that the Bureau of the Budget will, consistent with the President's message, give the matter prompt attention. Their objective is to place an Administration approved financing plan before the Subcommittee prior to the time of your "mark-up."

If possible, they hope to have a proposal in your hands before NIH completes its testimony—now scheduled for a week from today. This will depend on how quickly they can gather comments from other interested Departments and agencies.

Sincerely yours,

JAMES B. CARDWELL,
Deputy Assistant Secretary, Budget.

Mr. LAIRD. Anybody reading that letter will see very readily that it is an effort to delay submitting this material until too late to be discussed in these hearings. So I am going to have to ask you questions directly. I will ask these questions of you as the Director of the National Institutes of Health as one who has had long association with international health programs. I well remember your association with the World Health Organization to get programs going on there. I remember Mr. Fogarty's efforts at WHO to support that program even at the time the U.S. Government was supporting WHO's programs in the field of health and medical activities 100 percent.

I would like you to outline your views and your suggestions regarding the establishment of such an international center and also to outline fully the background of this concept for an international center at the National Institutes of Health. I realize that it is most important to have this outline by you. You have been Director of NIH longer than anyone else and you have had a longer association with this idea and the discussions surrounding it than anyone else. What you say will have great bearing on what this committee does in this 1968 budget.

Mr. KELLY. Could I comment before Dr. Shannon answers? I do not mean Dr. Shannon should not fully answer your question, but I think there is a misunderstanding as to the content of the letter sent to the committee. There is no interest on our part to deny the committee the information. Rather, what we have endeavored to do is to expedite executive branch consideration of the plans for this international center, which the President indicated would be transmitted to the Congress, in order that we could present it to you as the President's recommendation, and we still hope we will have this before you in order that you can consider it in acting on this budget.

Mr. LAIRD. Well, if it has not cleared the Bureau of the Budget at this time and if it has not cleared the State Department at this time, I would think it would not by the time this bill gets on the floor of the House. We cannot wait that long.

Mr. KELLY. We were unable to get it before the Bureau of the Budget until day before yesterday.

Mr. LAIRD. What do you have from State?

Mr. KELLY. That will be done by the Bureau of the Budget.

Mr. LAIRD. From past experience with the State Department that will take at least 6 months.

Mr. CARDWELL. It is my understanding the Bureau of the Budget has circulated the proposal to all interested agencies and Dr. Shannon and others have a meeting set up for Monday to go to the Bureau of the Budget to discuss the proposal.

DEPARTMENTAL PROPOSAL

Mr. LAIRD. Will you put in the record at this point what Dr. Shannon submitted?

Mr. CARDWELL. Yes.

Mr. LAIRD. And what you submitted to the Bureau of the Budget?

Mr. CARDWELL. Substantially the same. In substance they are substantially the same.

(The information follows:)

A PROPOSAL FOR AN INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

BACKGROUND

The proposal for the establishment of an International Center relating to the biomedical sciences at the National Institutes of Health has a number of antecedents. The earliest formal expression of such a possibility was the introduction by Sentor Hill late in the 85th Congress of Senate Joint Resolution 199 providing for the establishment of a National Institute of International Research at the National Institutes of Health. There was no action on this resolution in the 85th Congress. The same resolution was reintroduced by Senator Hill in the first session of the 86th Congress (February 2, 1959) as S.J. Res. 41, which passed the Senate in May of 1959. In addition to authorizing the establishment of a National Institute for International Medical Research as a part of the National Institutes of Health, this resolution provided for the encouragement and support of the "rapid international interchange of knowledge and information concerning disease and disability, including the holding of international conferences . . . and the support, on an international basis, of research training through fellowship and training grants."

The International Health Research Act of 1960

After extensive consideration by the House Interstate and Foreign Commerce Committee, including two series of hearings, S.J. Res. 41 was passed by the House in a substantially altered form and was enacted as P.L. 86-610, The International Health Research Act of 1960. Although the title of the Act still retained the statement "An Act to establish a National Institute of International Medical Research . . ." there was no provision for this entity in the actual terms of the law.

This new law, for the first time provided a clear distinction between the purposes to be served in providing support for research and related scientific activities beyond the boundaries of the United States. Two major purposes were cited:

1. To advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research and research training.

2. To advance the international status of the health sciences through cooperative enterprises in health research, research planning and research training.

Significantly the terms of the law separated the responsibility for the achievement of these two objectives. The responsibility for achieving objective (1)—

advancing the status of the health sciences in the U.S. through overseas activity—was given to the Surgeon General of the PHS and the Secretary of HEW. The exercise of authorities directed toward objective (2)—advancing the international status of the health sciences—was limited to the President but with provision for the delegation of this function to HEW and only to HEW.

Despite repeated approaches on the part of HEW, the President has made no general delegation of his authorities under this Act. In fact, only on two occasions has the President actually exercised these authorities; once in the award of a grant for research planning to the Pan American Health Organization in 1961; the other in the delegation to NIH in 1965 of authority to utilize funds in the execution of the Joint Japanese-American Life Sciences Research Program. The section of P.L. 86-610 to be administered by the President is pertinent in the context of the current proposal because it encompasses broad authority to establish and maintain fellowships in foreign countries and to finance international scientific meetings and conferences in the United States and abroad as well as to engage in other research support, training and assistance activities as the President may deem appropriate to achieve international purposes.

A center for advanced study

The establishment of a Center for Advanced Study at NIH—but with no particular reference to international considerations—was one of the recommendations contained in the "Final Report of the Study Group on the Mission and Organization of the Public Health Service" issued in June of 1960. In this Report the following statement was made:

"In view of the fundamental scientific orientation of the National Institutes of Health, better means and facilities are needed for encouraging advanced, creative, speculative thought, ranging across the full panorama of new findings and concepts emerging from current scientific endeavor which may have meaning in biology and medicine. Such opportunity would be afforded by the establishment of a Center for Advanced Study. This Center would permit the inductive exploration of these matters in an atmosphere removed from program, laboratory, and administrative distractions. Ideas and syntheses having basic impact upon the future development of the medical and biological sciences and the nature of health action in the future should emerge. Those with the ablest minds, inside or outside the Public Health Service, would be sought."

The Study Group responsible for the development of this report was appointed by Dr. LeRoy Burney who was then Surgeon General and had as one of its members Dr. William H. Stewart, the present Surgeon General.

Related ideas

President Kennedy frequently stressed the importance of an international approach to the solution of health problems. In his Special Message to the Congress on National Health Needs, on February 28, 1962, he said:

"It is imperative that we help fulfill the health needs and expectations of less developed nations, who look to us as a source of hope and strength in fighting their staggering problems of disease and hunger. Mutual efforts toward attaining better health will help create mutual understanding. Our foreign assistance program must make maximum use of the medical and other health resources, skills and experience of our nation in helping these nations advance their own knowledge and skill. We should, in addition, explore every possibility for scientific exchange and collaboration between our medical scientists and those of other nations—programs which are of benefit to all who participate and to all mankind."

The following year, in his Special Message on Improving the Nation's Health sent to the Congress on February 7, 1963, he said:

"We must continue our collaborative efforts with other nations in the global struggle against disease. Over the past few years the United States has rapidly expanded its international medical research activities and support. We have also been instrumental in encouraging research under the aegis of the World Health Organization. These efforts are consistent with and in furtherance of our goals of world peace and betterment, and it is important that they be continued."

In his address before the 18th General Assembly of the United Nations, on September 20, 1963, President Kennedy said:

"The effort to improve the conditions of man, however, is not a task for the few. It is the task of all nations—acting alone, acting in groups, acting in the United Nations, for plague and pestilence, and plunder and pollution, the hazards of nature, and the hunger of children are the foes of every nation. The earth, the

sea, and the air are the concern of every nation. And science, technology, and education can be the ally of every nation.

"Never before has man had such capacity to control his own environment, to end thirst and hunger, to conquer poverty and disease, to banish illiteracy and massive human misery. We have the power to make this the best generation of mankind in the history of the world—or make it the last."

The proposal of Representative John Fogarty

Mr. Fogarty presented his idea for an international center before the Third National Conference on World Health sponsored by the Citizens Committee for the World Health Organization, which was held in Washington on September 26, 1963. As the final point in his speech to the panel on Health for Peace, Mr. Fogarty said:

"In concluding my remarks I would like to set forth an idea and a view which I feel to be of the greatest importance and significance. Instead of a curtailment of the programs and activities of the United States in the field of international health research, I should like to see a plan to bring into being at Bethesda a great international center for research in biology and medicine dedicated to international cooperation and collaboration in the interests of the health of mankind as so boldly envisaged by the President. This center would encompass conference facilities, laboratory and study space, and living quarters to permit the assembly for discussion, study, and research of the outstanding health scientists of the world. I visualize this center associated with the great facilities of the National Institutes of Health and the National Library of Medicine as representing the visible and tangible embodiment of this Nation's devotion to the use of science for peaceful purposes and the good of mankind."

Shortly after this speech Mr. Fogarty urged consideration of this idea in a letter to the Secretary of Health, Education, and Welfare (Mr. Celebrezze). The Secretary's response was favorable and indicated intentions to consider a budgetary request for this proposal.

Support by Senator Humphrey

Mr. Fogarty's idea of an International Center gained the immediate support of Senator Hubert Humphrey who included it in a nine-point health program which he described in a speech on the floor of the Senate on October 14, 1963. Senator Humphrey said:

"Congress should make specific provision for an International Medical Conference Center. Such a Center would greatly facilitate NIH's international program.

"It would end the deplorable embarrassment which U.S. Medical leaders chronically and inevitably experience because conference facilities are so sadly lacking.

"The Center would cost around $4 million. Through it, both NIH and the National Library of Medicine would have for the first time the resources to bring together scientists to share their experiences under the most favorable and timesaving conditions.

"It is a regrettable paradox that in spite of the extensive participation of the United States in international medical affairs and the desirability and probability that this involvement will increase, there is no place in the United States available for the efficient conduct of medical meetings, symposia, and working seminars attended by scientists of different countries.

"While the National Institutes of Health is a medical research center which attracts hundreds of people from foreign countries every year, it has no facilities equipped, for example, for simultaneous translation and for suitable conduct of this important aspect of medical research.

"This issue has been discussed in the Senate and House Appropriations Subcommittees. I earnestly hope that my colleagues in both Houses will support what I believe is the sympathetic interest of these subcommittees toward establishing such a center."

Discussion in appropriation hearings

In the development of budget requests for fiscal years 1965, 1966, 1967 and 1968 the National Institutes of Health presented estimates for the construction of an International Conference Center which did not survive the budget review process. Mr. Fogarty, however, continued to press his interest in this concept. In February 1965, during the course of the appropriation hearings, he asked Dr. Shannon, the Director of the National Institutes of Health, to describe the need

for such a center in connection with a discussion of site planning for the Bethesda campus. The following is an excerpt from the hearing transcript:

Dr. SHANNON. [Stone House] is now being used for conference space. What we have talked about—it is not before you as a serious proposal today—is its use as the base for the development of an international conference center. We feel that perhaps one of our most important contributions to the international framework of science could be made through the give and take of a seriously developed series of continuing seminars. When I say continuing seminars, I mean the consideration of individual work areas continuing over a period of some years, thus permitting the development of certain action programs where certain plans could be initiated, and more than a single nation could address itself to the problem.

Mr. FOGARTY. What are the possibilities?

Dr. SHANNON. To set up an international conference center, there are three possibilities. There is a possibility of having a motel to be run by a private contractor. There is a possibility of contracting with some organization to run an entire conference building, including eating facilities, housing facilities, and the like, not subject to the restrictions that we would have. Or is it possible to run a center without living accommodations and depend upon the surrounding area for support? I do not believe, sir, that the latter is possible.

There are motels around, but if one is going to make a conference activity of this sort operate effectively, one has to create the atmosphere not of isolation, but of separation, so that the individuals who attend the conference can interact with each other throughout the entire day and evening or a series of days. One cannot break up to go to widely separated hotel rooms or eat in a wide variety of scattered places and maintain, effectively, the continuity of the discussions.

I do not want to pursue these possibilities now, but I think that ultimately such conferences could be an important function of the National Institutes of Health. It could be constructed in this area [indicating] and might involve Stone House as a clubhouse-type facility that would be integrated into the remainder of the conference setup. There is a serious need for this type of resource.

Our Office of International Research is running an international conference at the end of this month. The conference will involve about 15 participating countries. The subject will be the structure and processes by which these countries develop national policies for biomedical research and determine the level of expenditure, allocate funds to various kinds of research, the frame of reference within which these expenditures are made, and so forth. This is not a philanthropic activity on our part. We want to profit from the experience of a diversity of countries and see the effects of a diversity of mechanisms.

This conference will involve about a hundred people. The nearest place where we can obtain adequate facilities for such a conference that has the separation, or partial isolation, I spoke about is Williamburg. I would like to have these very distinguished scientists and science administrators come to Bethesda and meet on the campus of the National Institutes of Health.

The point is that there is not, in Washington, a wholly suitable place. There is an equally serious need for the Bureau of State Services, for example, to have something of this sort. This facility is needed, not simply to satisfy the needs of the National Institutes of Health, but to satisfy the needs both of various units of the Public Health Service, as well as those of other governmental agencies seriously engaged in science. There should be some place where we can provide the right atmosphere for what you might call a scientific retreat. There, literally, is no such place.

The proposal of Representative Melvin Laird

John Fogarty died on January 10, 1967, the opening day of the 90th Congress. The House of Representatives designated January 18, 1967, as the day on which eulogies in memory of John Fogarty would be received. During the couse of this day's proceedings Representative Melvin Laird (Rep. Wisc.) made the following statement:

"Mr. Speaker, John Fogarty's deep and devoted interest in international health and his conviction that through international exchange in the health sciences, a significant contribution could be made not only to the solution of health problems but also to the advancement of world peace is perhaps, best epitomized in his remarks before a panel on Health for Peace during the meeting of our Citizens Committee for the World Health Organization held in Washington in September 1963. The final paragraph of John's remarks is of particular significance and I should like to quote it here:

[The quote referred to is the same as that found on page 5 above.]

"I can think of no more fitting and lasting tribute to this great humanitarian than the establishment by this Congress of such a center—the John E. Fogarty International Center for Advanced Study in the Health Sciences. I have talked with most of the members of our committee about this and they have all been enthusiastic in their support. I am sure that support will be unanimous, both in our committee and in the entire Congress. Not only will such an institution be a living embodiment of the spirit and aspirations of John Fogarty, but it will serve a needed and valuable role in securing the progress of science in the cause of the well being of all mankind."

In private conversations Representative Laird has repeatedly emphasized his firm intent to pursue this concept. He had indicated his desire to have the funds for the construction of this center included in the Labor-HEW Appropriation Bill for FY 1968.

The proposal of the President

The President in his Message to Congress on Education and Heath in America made the following statement:

"I am seeking funds to establish an International Center for Advanced Study in the Health Sciences and to provide scholarships and fellowships in the Center."

It would appear that by this statement the President was indicating his full conceptual concurrence in the need for an International Center as part of the NIH. However, it has been stated that the Office of the President was of the view tht the designation of the Center as a memorial to John E. Fogarty, as proposed by Mr. Laird, was an action more appropriately to be taken by the Congress.

Other support for the International Center

The propoosal for the establishment at NIH of an International Center for Advanced Study in the Health Sciences as a memorial to John Fogarty has received broad support in many quarters. Particularly noteworthy amongst the many favorable comments made on this idea was the quoting of Representative Laird's proposal in an editorial in "Science" magazine written by Philip Abelson, the Editor. Mr. Abelson noted that this proposal would be supported by many scientists because of the great awareness in the scientific community of the significant role John Fogarty played in the advancement of the biomedical sciences.

Finally, the various National Advisory Councils have long and repeatedly stressed the inappropriateness of a purely domestic role for NIH and the great scientific and national benefit that would accrue from a more vigorous international activity under NIH sponsorship. A variety of statutory, monetary policy, and budgetary considerations have thus far intervened to limit the scope and magnitude of NIH international functions.

THE PROGRAM OF THE INTERNATIONAL CENTER

The concept of the International Center as it emerges from the above backgrounds encompasses three basic ingredients. First, its role should be international in scope and mission, dedicated, as Mr. Fogarty envisioned, "to international cooperation and collaboration in the interest of the health of mankind." Second, the subject matter of its concern should be the international advancement of the health sciences broadly viewed. Third, its purpose should be to provide the appropriate setting and facilities for advanced study "to permit," as Mr. Fogarty put it, "the assembly for discussion, study, and research of the outstanding health scientists of the world."

The functions which are proposed below for the International Center encompass the major thrusts of these distinguishing elements. However, there is the further purpose of utilizing these functions for the evolution of a program which, in the long run, will exert a profound influence on the overall development of medicine and the biomedical sciences internationally as well as in the United States. Consequently the initial formulation of the activities of an "International Center for Advanced Study in the Health Sciences" must take into account two considerations: First, to allow for the progressive clarification of the unique and essential role to be performed by such a center in the prospect of this long term purpose; secondly, the development of an organizational framework and operating guidelines sufficiently general in character to be responsive both to the needs of this Nation and the character of international scientific activity as

they may change over the years. Thus with these considerations in mind, it is proposed that initially the International Center encompass the following basic functions:

1. The support of scholars for advanced study

The study of biological phenomena as a base for the advance of medicine and health has broadened enormously in scope and become ever more penetrating in depth during the past two decades. The diversity of this scientific endeavor, the enlarging comprehension of the nature of basic biological activity and the relevance of other fields of science thereto have developed at an astounding rate during this period of time. The critical importance of this area of knowledge to the future course of human affairs has generated the need for special arrangements to encourage the development of broad, embracing syntheses of this rapidly expanding knowledge and the evolution of simplifying theoretical concepts that will only be derived from speculative and creative thinking. Many of the fundamental, complex and intractable problems and uncertainties confronting the advance of these sciences and their relationship to human affairs might be made to yield through bringing to bear the concentrated effort of the best scientific minds working in close relationship over a given period of time. In addition, there is great need to expand and deepen the tentative beginnings of an interface between the advance of biological science and the movement of the social and behavioral sciences. These developments have far-reaching import for the structure of medicine and the framework of health services. But more importantly, man's growing ability to manipulate and control the conditions of life and the very basis of the evolutionary process poses grave implications for the nature of social institutions, the basic concepts of law, and the character and adequacy of decision making processes in a democratic society in the future. Activity of this kind requires an atmosphere conducive to inductive thought in an environment free from program, administrative, and laboratory responsibilities.

Thus a primary function of the Center would be to create for the health sciences an institution dedicated to advanced study comparable in broad outlines to the Institute for Advanced Study at Princeton, New Jersey, and the Center for Advanced Study in the Behavioral Sciences at Stanford, California. It is envisaged that this function would involve provision for the maintenance of from 15 to 30 outstanding scientists, scholars, or other individuals of intellectual distinction (it is estimated that perhaps only 15 of these individuals would need to be actually housed in the Center facility; others may prefer to reside in private residences). These individuals would be chosen by an Advisory Board to the Center for periods of residence ranging from one to five years.

Full maintenance would be provided for these scholars plus travel and other expenses associated with their activities in the Center. Arrangement would be made to provide convenient access to the laboratory facilities of NIH or other Federal research facilities and to the services and facilities of the National Library of Medicine as may be required by the scholars. The Center would encompass facilities for study, discussion, and the essential residential, social and recreational amenities.

Recognizing the intimate association of Representative Fogarty and Senator Lister Hill in the active promotion of biomedical research for the advance of medicine and health, appointees to this program might well be designated as Fogarty-Hill Scholars (or Associates) of the International Center.

2. An international fellowship program

In addition to the Scholars in Residence Program it is proposed that the Center administer an international fellowship program to provide support for the broad international exchange of individuals for teaching, research, and study in the health and related sciences. These fellowships would be of two levels:

(a) A series of awards on an international basis to encourage the international exchange of senior teachers and scientists amongst universities and research institutions in foreign countries as well as between the United States and foreign countries. These awards would provide full salary, research and living costs and would be on a two to five year basis. Approximately 100 of these awards, to be known as John E. Fogarty Professorships, would be available.

(b) A series of fellowships to support the study of pre- and post-doctoral students in the health sciences outside the borders of their native lands. This program would encompass the present International Postdoctoral Fellowship Program of the NIH but would be broadened to provide for both

American as well as foreign participants. Approximately 300 of these awards would be made available. Perhaps recognition of the instrumental role played by Representative Frank B. Keefe (R. Wisc.) in the initial evolution of NIH programs during his chairmanship and service on the Appropriation Subcommittee, 1945–1950 could be given by designating these awards as Frank B. Keefe Fellowships.

The latter activity would not be intended to substitute for the award of fellowships to U.S. nationals for study abroad which are an essential element of the program of each operating division of NIH.

3. International conference and seminar program

The final act in the procedure of science is centered in the process of communication—publication and discussion. The rapid growth and expansion of the biomedical sciences has generated enormous pressures on the communicative process in terms of its adequacy and scope.

In the area of publication the response to these pressures has been the elaboration of scientific journals and publications and other devices for the management and dissemination of scientific findings via the printed word. Information of this type is being adequately handled in general in most areas and steps to remedy existing deficiencies are being taken by a number of agencies (OST, FCST, NLM, etc). Such literature, however well handled in general, is inevitably concerned with what has passed in science, that is, what has been accomplished. It does not provide the adequate means for enlightened interchange on the future of science both in terms of substantive opportunities that are not immediately apparent and the broader implications of developing scientific trends.

The area of discussion has been marked by the proliferation of scientific meetings randomly developed, of diverse character and involving large segments of activity of questionable utility or value. The National Institutes of Health as well as other programs of the Public Health Service are extensively engaged in both the initiation and support of such conferences. However, these activities lack coordination and effective management. Thus there is urgent need in the biomedical sciences for the development of a deliberately organized, carefully planned program of conferences, seminars, and working scientific sessions developed around the major scientific problems, opportunities, trends, developments to facilitate the progress of knowledge and to explore its implications for society. The character of these conferences would be quite different from the current international professional meetings.

Beyond the need for effective organization of and better content for conferences and scientific meetings there is the fundamental requirement of adequate physical facilities for such purposes. The present conference facilities of NIH, and indeed those that are reasonably available on a rental basis, are inadequate to meet the size and character of present conference needs much less those which might arise out of a well organized program. Thus the plan of the proposed Center would provide space for intermediate sized meetings, working conferences and seminars as well as study and discussion groups. Flexibility of space and adequate facilities for simultaneous translation, recording, and for audiovisual displays would be integral to the plan. One large meeting space to hold up to 300 persons is proposed. This would be designed to permit flexible use, i.e., to be subdivided into smaller meeting areas and to be utilizable for banquet and other social purposes.

4. The coordination of foreign visitors

The flow of distinguished foreign scientists, guest workers and health administrators from other countries, representatives of other governments, and other foreign visitors to NIH requires a point of reception capable of managing the language needs, the official documentary and regulatory problems (passports, alien registration, income tax requirements, etc.), housing needs and arrangements, transportation and program scheduling in a competent, organized and coordinated manner. Thus, it is proposed that the Center serve as the central point for the reception and management of the large number of foreign scientists and other international visitors to the National Institutes of Health. A program for this purpose would be one of the basic operating activities of the Center.

More importantly such an arrangement would permit gaining the maximum benefit from the foreign talent now visiting NIH. Broad notification of visits, providing for wider attendance of seminars, discussions and meetings centered around such visitors, engendering broader interchange of activities which would

contribute to the most effective use of time and capability of foreign visitors. A minimum staff with appropriate language and procedural knowledge would be provided for this purpose.

The above elements would compose the major functions proposed for the International Center. The Center could with time serve a substantially broader international role by serving as the instrument to carry out all the functions encompassed in the authorities made available to the President under P.L. 86–610. This matter presents a number of questions which need greater exploration or some operating experience before conclusions on such a broader role could be reached.

FUNDING REQUIREMENTS AND SOURCES

The proposal for the International Center for Advanced Study in the Health Sciences encompassing a program as outlined above is estimated to require a facility for the main structure which would provide approximately 123,000 gross square feet. This structure would provide for the following:

6 conference rooms for 50 people each.
6 conference rooms for 200 people each.
1 conference room for 100 people.
Auditorium for 300 people.
Translating facilities.
Reference and reading room.
Exhibit space.
Reception lounge.
Lobby and reservation area.
Office space for a staff of 200.
15 living apartments for distinguished scholars-in-residence.
25 overnight sleeping units.
Cafeteria with seating for approximately 300 persons.
Multilevel parking for 400 cars.

The estimated cost breakdown for the construction of this facility is as follows:

Land acquisition	
Planning	$820,000
Construction	9,330,000
Total	10,150,000

A preliminary analysis of the detail of these construction costs is contained in an attachment to this document.

These estimates exceed prior calculations of the cost of an International Conference Center at NIH by a substantial amount. These increased cost are due to the following factors:

a. Broadening the scope of the proposed facility to encompass a scholars-in-residence program and the administration of additional operating activities such as International Fellowship Program and the coordination of foreign visitors to NIH.

b. The development of a design and architectural form of high quality consistent with the international stature of the activity and its identification as a memorial to the late Representative Fogarty.

c. Expansion and addition of service elements related to the cafeteria, multi-level parking, reference, reading and reception facilities.

d. Increased material and construction costs since the time of previous estimates.

The estimated operating costs for this facility must be viewed as very tentative since full details of the operating programs have not been entirely fixed. Current estimates are as follows:

The scholars-in-residence program	$1,500,000
The fellowship program	7,250,000
The international conference and seminar program	2,000,000
The foreign visitors reception and management program	500,000
Program direction and management costs	1,500,000
Total	12,750,000

Not all of this amount would represent increased appropriation since some current NIH activities, e.g., the International Postdoctoral Fellowship Program,

would be transferred to the Center. A preliminary rough estimate of such existing expenditure would total $2.0 million.

Furthermore this total represents overall operating costs at the time all programs have reached their full operating level. It is expected that the development of these programs will be spread over a period of from three to five years. Thus the phasing of operating cost requirements might run roughly as follows:

Fiscal year 1968: The assembly of staff and costs of initial arrangements	$750,000
Fiscal year 1969: Initiation of program	3,000,000
Fiscal year 1970	7,500,000
Fiscal year 1971	10,000,000
Fiscal year 1972	12,750,000

The source of funding for the planning and construction and initial operating costs is visualized as follows:

a. It is proposed that some part if not all of the planning monies for this Center be sought through reappropriation of unobligated fiscal year 1967 balances in NIH program accounts. This would permit immediate initiation of planning activities.

b. Full construction costs be sought as a supplement to or an amendment of the President's Budget for fiscal year 1968.

c. These additional operating funds required for expenditure in fiscal 1968 would also be sought as a supplement to or an amendment to the President's 1968 budget.

ORGANIZATIONAL AND PROGRAM RELATIONSHIPS

It is proposed that the International Center for Advanced Study in the Health Sciences be located physically in Bethesda, Maryland, on the grounds of the National Institutes of Health. A suitable site east of the present Stone House building and west of the Library of Medicine is available for this purpose.

It is planned that the International Center would be established as a component of the National Institutes of Health under the general supervision of the Director, NIH. Its plan of operation should provide for a Board of Advisors appointed by the President upon recommendation by the Secretary, reflective of the Federal, scientific and international interests to be served by the Center. The Center should be administered by a director chosen from candidates recommended by the Board. The position of the Director should be excepted from the Classification Act with a salary adequate to command the best talent in the Nation. There should be adequate provision for supergrade or other excepted positions for the supporting staff of the Center.

The operating arrangements for the Center should provide for close working relationships with the National Library of Medicine and other Federal facilities in the Washington area. Further details on the operating plan for the conduct of the Center are in process of preparation.

It would appear that no new legislative authority is required for the conduct of the programs of the Center if full use is made of the Presidential authorities contained in P.L. 86-610.

Mr. LAIRD. Is there anything you wish to add at this time that is not in the material which has been inserted in the record?

Dr. SHANNON. I understand that the Department is going to send you a document that is called proposal for an international center for advanced study in the health sciences, which is basically the document we sent to the Department. This traces the development of the need, the development of the idea, and mentions the individuals and events that have contributed to this development starting with Senator Hill in 1959, the International Health Research Act of 1960, the report of the group appointed by Dr. Burney to advise on the reorganization of the Public Health Service which pointed out that there was a need for an advanced study center.

It quotes Mr. Fogarty's statement of 1963, and, I believe, some comments relative to the importance of international research to inter-

national relations by President Kennedy, Senator Humphrey's endorsement of John Fogarty's proposal, and then some of the discussions we had here in the appropriation hearings.

I think it contains the whole historical background. It then touches on how the Center should be supported, what its program should be, and roughly what it would cost.

I think it is a very complete document that will stand on its own feet.

LETTER FROM DR. ROBERT C. BERSON

Mr. LAIRD. I would like placed in the record a letter I recently received on this subject from Dr. Robert Berson.

(The letter follows:)

ASSOCIATION OF AMERICAN MEDICAL COLLEGES,
Washington, D.C., March 29, 1967.

Congressman MELVIN R. LAIRD,
House of Representatives,
U.S. Capitol,
Washington, D.C.

DEAR CONGRESSMAN LAIRD: When John Parks and I had the pleasure of being with you on February 15th, you indicated you would welcome suggestions about the proposed John E. Fogarty Memorial. In the interest of saving your time, I want to pass on our suggestions in writing, although we would, of course, be delighted to discuss it at any desired length. We have had some opportunity to discuss this matter with our colleagues on the Executive Council of the Association of American Medical Colleges, and know that they share our views.

In our opinion, a very important and large part of this memorial should be a program of "Fogarty Fellowships" which would make it possible for members of the health team now in U.S. institutions to spend periods of study or research at NIH or in institutions in foreign countries, and for individuals now in foreign institutions to spend periods at NIH or in U.S. institutions. We think it would be useful if the terms were broad so that the fellowships would be available not only for senior medical scientists but also for members of the team at all stages of their development. There is a rather high degree of interest among medical students, residents and younger members of the faculty in U.S. institutions in opportunities to learn about and contribute to health problems in other lands. Some of us are convinced that such opportunities when the individual is relatively young, have a more constructive influence on his later development and attitude. A good many individuals find it difficult to adjust to, or make maximum utilization of, such opportunities when they are relatively late in their careers. It now seems quite clear that there are numbers of members of the "health team" such as nurses, physiotherapists, medical technologists, hospital administrators, health economists or medical sociologists who can make contributions through, and benefit from, such opportunities. No doubt, most of the fellowships should go to medical scientists or physicians, but we would hope that terms of reference of the program are sufficiently broad for fellowships to be awarded to some other members of the health team.

John Fogarty was explicit in expressing an interest in an international center at NIH. We believe that a part of the memorial to him should be such a center, that it should provide reception facilities for visiting scholars, probably including temporary quarters and food services, as well as facilities for conferences, seminars and lectures. We hope NIH will recommend that a staff be organized to receive such visitors to plan an organized program of lectures, seminars and conferences, and that the present program of international postgraduate awards be administered through this staff. These things seem sound and desirable to us.

Finally, we believe that a suitable memorial to this great American should be a substantial and stable program which can grow as its usefulness is demonstrated.

Sincerely yours,

ROBERT C. BERSON, M.D.,
Executive Director.

PROPOSAL FOR EYE INSTITUTE

Mr. LAIRD. Dr. Shannon, I have been receiving quite a few letters from doctors and scientists and various people who have dealt very closely with the National Institute of Neurological Diseases and Blindness. They are concerned about the efforts being made in some quarters to divide this Institute.

As you know, some people want to create a separate Institute on Hearing, a separate Institute on Sight, a separate Institute on Speech, a separate Institute on Muscular Dystrophy, a separate Institute on Parkinsonism, a separate Institute on Multiple Sclerosis, a separate Institute on Mental Retardation. Most of the activities in these fields I have named—and I have named just a few of them—are now the responsibility of the National Institute of Neurological Diseases and Blindness.

I wish you or someone on your staff could spend some time educating the people who want to divide these Institutes. Take them out there and show them how the National Institute of Neurological Diseases and Blindness actually operates.

When you start dividing these Institutes into separate Institutes, just from my experience on this committee since the Department of Health, Education, and Welfare was created, you run into tremendous administrative expense. What is the administrative expense, without doing a bit of research, involved in the creation of a new Institute?

Dr. SHANNON. I have looked into that in relation to this proposal. It costs about $300,000.

Mr. LAIRD. Just to pay the Director and his immediate staff?

Dr. SHANNON. And to get intramural teams and to provide the apparatus to develop a program and ride herd on even a small program.

Mr. LAIRD. I understand some legislation has been introduced to divide out the sight work or the eye work.

Dr. SHANNON. There has been, indeed.

Mr. FLOOD. There were about 50 or 60 bills in the House and more in the Senate.

LETTER FROM DR. PAUL C. BUCY

Mr. LAIRD. A great deal of effort is being made to get individuals to introduce these bills. It concerns me. I have a letter in my hand from Dr. Paul C. Bucy, professor of surgery at Northwestern University Medical School, a very thoughtful letter which I would like to put in the record at this point, in which he explains the difficulties of this idea of continuing to create separate Institutes out there. I would like you to discuss this a little bit from the standpoint of your background and experience with the National Institutes of Health.

Mr. FLOOD. I think that letter should go in the record. I have one, I imagine pretty much the same letter.

(The letter follows:)

CHICAGO, ILL., *February 10, 1967.*

Hon. MELVIN LAIRD,
House of Represesentatives Office Building,
Washington, D.C.

DEAR CONGRESSMAN LAIRD: It has come to my attention that a determined effort is again being made to subdivide the National Institute of Neurological Diseases and Blindness (NINDB) by creating a separate Institute concerned with eye diseases. For almost 15 years I have been associated with NINDB in an advisory capacity. I believe that this experience has provided me with an above average understanding of the operations of that Institute. Of course, my associations with the Institute have always been as a civilian outsider, not as a member of its administration or staff.

In my opinion the establishment of a new Institute to deal with eye diseases would be undesirable. The eye is intimately related to the nervous system. Except for conditions within the eye itself it is seldom possible to separate consideration of the eye from that of the nervous system. Basic research concerned with disorders of the eye and those of the nervous system are inseparable. An understanding of the eye itself and of its diseases requires an understanding of the nervous system. It is rational and desirable, therefore, that the Institute concerned with research having to do with the eye and the nervous system should be one—not two. Should a separate Institute for the eye be established the greatest loss would be to those concerned with the eye, not those concerned with the nervous system. Nevertheless, there would be a loss to both.

NINDB has been an extremely well administered Institute. It has never shown even the slightest prejudice or preference for any of the component disciplines with which it is concerned—neurology, neurological surgery, ophthalmology, otolaryngology. In other words, the eye and its diseases has never suffered from being the concern of this Institute.

To establish another Institute would require the creation of another complex administration within NIH. This would necessitate an additional large expenditure of public funds to create an unnecessary additional administration for this new Institute. This is probably the least important of the considerations, but it is not an unimportant one.

If I believed that ophthalmology would benefit by the creation of a new Institute I would support it, but I do not believe this is the case.

Though must also be given to further expansion of this tendency. If a new Institute is to be created for ophthalmology should other separate Institutes be created for otolaryngology and for neurological surgery? I believe this effort to divide NINDB should be avoided.

Should you desire I would be happy to discuss this matter with you at any time.

Sincerely yours,

PAUL C. BUCY, M.D.,
Professor of Surgery (Neurosurgery),
Northwestern University Medical School.

Mr. FLOOD. As a matter of fact, Doctor, in case Mr. Laird is not aware of it, I believe you met as recently as yesterday or the day before at a conference with 15 or 20 Members of the House who introduced this bill, did you not?

COMMENTS ON PROPOSAL BY DIRECTOR OF NIH

Dr. SHANNON. Yes. Two days ago Assistant Secretary Lee, Assistant Secretary Huitt, and I met with Senator Hill, who is one of the sponsors of this legislation in the Senate, to discuss the advisability and the need for an expanded program, and the inadvisability of setting up a separate administrative organization to accomplish this objective.

Yesterday, at the request of Representative Young of Texas, we had a somewhat similar conversation. I would judge there were 10 or 15 Members of Congress who had an interest in this legislation

who met with us. Again we pointed out the need for an expanded program and the inadvisability of doing this as a separate activity.

We made three points. The first is that simple organization of an institute, in and of itself, does not provide a better mechanism for programs that can be provided within an established institute. On the other hand, it creates difficulties because one has to start from scratch in the acquisition of personnel, which is very difficult to do these days, and, if anything, it delays the development of the program.

The second point we made was that eye research in this country has fared very well within the programs of the National Institute of Neurological Diseases and Blindness. I pointed out to them that, in recent years, there has never been a shortage of funds that precluded our giving preferential treatment to eye research. I indicated to them that, in contrast to the 24 to 26 percent of the grant applications that are funded in the general program, in the blindness area the percentage was 36 percent.

The interesting thing is that the high percentage of high-priority eye-research grants is attributed to the training program that has been going on in the eye field ever since the establishment of the National Institute of Neurological Diseases and Blindness. We reviewed one of the recent numbers of a journal devoted to research in ophthalmology, and it turned out that the bulk of scientific advances reported in this particular issue were as a result of grants and fellowships derived from the National Institute of Neurological Diseases and Blindness.

Finally, we said that we had reexamined the Institute setup at the time it was proposed by the President's Office that we set up an Institute for Mental Retardation, in 1961 or 1962. We reviewed our coverage of the entire biomedical field, together with the underpinning of fundamental science. We came to the conclusion that we should create two Institutes, and that when we had done that we would really cover the field in a reasonably logical pattern. We convinced the President's Office that, instead of setting up an Institute of Mental Retardation, we should set up an Institute which addressed itself primarily to problems of human development and which would cover both ends of the time spectrum of life. We felt that within such an Institute it would be possible to develop a vigorous program in the field of mental retardation.

We pointed out to Senator Hill and Representative Young that we had the mechanisms available for research on blindness. The level of that research depends upon two things, really: One is the dollar level that will be made available for research and training in this area, which has been adequate to the present time but may not be adequate in the future, the other is whether the Congress chooses to create a substantial increase in eye-research resources by making available preferential matching for a construction program. This is what made the mental retardation program go. We pointed out that the Department had, indeed, proposed preferential matching for a limited number of areas of national concern that were not developing as a result of the normal grant procedure and the normal 50–50 matching. Such preferential matching was agreed to by the Senate but the House Interstate and Foreign Commerce Committee decided to limit construction to 50–50 matching.

Mr. LAIRD. We have discussed that here in this committee, too.

Dr. SHANNON. Yes, sir.

Given adequate construction funds, we feel that we have all the program authority in NINDB and in other elements of the Public Health Service to develop a program that involves academic opthalmology, research in opthalmology, and the fundamental sciences upon which it depends. The Public Health Service has ample authority to develop programs in that area. In other words, we think we have the necessary authority.

We think we have demonstrated within the Institute of Neurological Diseases and Blindness that special programs can be developed. We feel that to do it by a separate Institute would set a precedent and would lead to pressure to create many others. The gastroenterologists are very anxious to have a separate Institute. I could mention a whole array of them.

I think if this course is selected, NIH in its present guise will disappear, and we will become a large number of fragmented activities, basically uncontrolled.

I said this to Senator Hill and Mr. Young. We left with them a document that outlined what we felt to be a reasonable way to develop a program.

Mr. LAIRD. I think somehow or other we must try to get these people who are interested to have a better understanding of what is going on in NIH, and that it is not in anyone's interest to fragment the Institutes.

That is all, Mr. Chairman.

Mr. FLOOD. Mr. Smith.

BASIC MANAGEMENT PROBLEMS

Mr. SMITH. Doctor, yesterday and earlier today some references were made to the matter of having adequate attention given to basic management problems. Principally what I was referring to were reports and conclusions that were based on operations 2 or 4 years ago. What major activities or actions have you taken since 1962 to overcome these management problems?

Dr. SHANNON. The first action was to codify and publish—perhaps in too much detail but be that as it may—all of the regulations covering each of the programs so that every administrator, grantee or applicant would know precisely what they were. In so doing, we were able to clarify any variations in the interpretation of what was the rule or regulation or policy that obtained for PHS or NIH across the board.

This led to a series of regional meetings with the administrators of a large number of institutions we serve where these regulations, which were shortly to be promulgated, were discussed in great detail and where any misunderstandings as to language were ironed out. Then the rules and regulations were recast.

In so doing we reserved to ourselves certain decisions that had theretofore been made by the grantee institutions. These related to certain forms of travel, certain purchases of equipment, and the shifting of funds among categories of expenditure—from personal services to other objects, and things of that sort. Central permission must be obtained and recorded as a desired change in the central system. So

that, mechanically, one would have thought our house was in order and that no problem would be encountered from then on. This did not, in fact, turn out to be the case.

Having reserved unto ourselves such a large number of operating decisions—each one of which involved only a small dollar expenditure but which, in the aggregate, amounted to a large number of dollars—we found that this placed us in a position of attempting to make decisions in Bethesda that really were more appropriately made by a competent group within the university itself.

Mr. SMITH. What kind of decision?

Dr. SHANNON. Such as whether another spectrophotometer was needed. There might be one next door. The type of decision that involves an expensive piece of equipment that might be used by several departments that should be considered by the several departments rather than by an individual. We decided that these were decisions that assumed knowledge on the part of the administrators in Bethesda beyond what they could have. They were doing it as best they could, and were using the postaudit as a means of checking on the consequences. We decided to select six universities, which had competent accounting systems and stable well-defined executive groups, and arranged with them, for a trial period, to set up a review system within their own university to serve as our agent for the review of these requests so that the investigator could go, not to his boss, but to a committee that would exercise responsibility.

Mr. SMITH. In that university?

Dr. SHANNON. In that university; yes, sir. Six were selected—Rockefeller, the medical school at Hopkins, University of Michigan, University of Pennsylvania, MIT, Columbia University Medical School, and one hospital that is heavily engaged in research—Massachusetts General.

This was watched very carefully. At the end of a little over a year it was decided that this might well be a much better method. Control within the institution, with records made of the decisions and how the decisions were reached, would result in a more efficient expenditure of money than if we were to make the decision on the basis of inadequate information.

We believe that this type of system is good and we are considering whether it cannot be extended to include more institutions.

Mr. SMITH. How long has this system been in effect?

Dr. SHANNON. We are near the end of 2 years.

Mr. SMITH. Under that system, how would you determine that the request for equipment or travel funds or whatever it may be is something needed by the investigator rather than merely replacing funds the university would have had anyway?

Dr. SHANNON. Well, Mr. Smith, it is a very difficult decision to make, under any circumstances, as to whether funds are available for a piece of equipment from other sources or only from us. I do not think we can make that decision. I think that if the decision is made and documented by competent people that a piece of equipment is needed for some particular work and that there would seem to be no other source of funds, I do not think we can go beyond that.

Mr. SMITH. And they will certify then that the piece of equipment is needed by the investigator?

Dr. SHANNON. The executive group will record these decisions and the reasons for them.

DECISIONS TO FUND CONTINUING GRANTS

Mr. SMITH. Suppose a grantee has completed the second year, how do you decide if the requested money for the third year of the grant is needed? It is a continuing grant?

Dr. SHANNON. If, for example, the initial commitment was made for 3 years, further payments, after the initial period, will be largely on the basis of expenditures. In other words, they are not allowed to accumulate balances. We have moved into a very complex system of payment that is on a cash-demand basis and that tends to hold money within the Federal Establishment rather than puting it out and letting it rest until used.

Mr. SMITH. Does it not also involve whether they used the money as intended the previous year?

Dr. SHANNON. Yes, sir.

Mr. SMITH. How do you determine how much they need for the third-year grant or that it should be given, or in other words, that the money was spent properly the second year?

Dr. SHANNON. We know the progress that has been made.

Mr. SMITH. But you do not receive that report until 3 months after you have awarded a grant for the third year?

Dr. SHANNON. The actual grant is made but payment is made virtually as the expenses occur. This gets a little complicated. I would like to have our administrative and fiscal people describe how it works in precise terms because I am not a fiscal expert.

Mr. FLOOD. Who is the right man to answer that?

Mr. MILLER. One point I would like to make is that we get a quarterly expenditure report.

Mr. SMITH. Do you have a review of what was done in the second year before you make an award for the third year?

Mr. MILLER. We know what the expenditures are for.

Mr. SMITH. Do you know that they spent them as intended?

Mr. MILLER. There are selected site visits, and there are audits.

Dr. SHANNON. On a 6-month-to-6-month basis we do not know precisely what each of the grantees is doing. But it is well established both in practice and the guidelines that generate the practice, that if there is a change in the project from the general purpose for which the funds were requested, then they must reapply—if there is any drastic change.

Mr. SMITH. How much of a change in personnel is required before they have to reapply?

Dr. SHANNON. In general, the grants are made in support of a principal chief investigator. There may be substantial changes in supporting personnel without reporting to us.

Mr. SMITH. While there is a principal investigator in a project you also consider others working with him in determining the real competence of this team. How do you know that in the second year half of them did not get a contract with somebody else and leave the project

with a lower grade team or one not as competent as the one to whom the grant was made?

Dr. SHANNON. The responsible investigator has a great degree of freedom in the personnel employed. The only penalty he suffers if he loses his competence is when his grant comes up for renewal.

Mr. SMITH. When he comes up for renewal, is he penalized for reducing competence or is he given a renewal anyway?

Dr. SHANNON. He is given a renewal unless we have reason to believe he has lost his capability. In general, the responsible investigator serves, if you will, as our agent for the responsible expenditures of the funds for the purpose for which they were granted.

Mr. SMITH. Under the review procedures do your records indicate whenever he has lost a substantial amount of his supporting personnel?

Dr. SHANNON. It would be shown on renewal, at the end of a committed period of support. We do not insist that they do so on an annual basis.

Mr. SMITH. Have there been examples where you denied further funds to the grantee because he had lost supporting personnel?

Dr. SHANNON. I cannot tell you how much, but I know that a substantial number of grants are not renewed beyond the initial period of support. I would assume some of that is because personnel was deemed to be inadequate.

Mr. SMITH. But your procedures are not such that you can be sure he has continued to provide adequate supporting personnel?

Dr. SHANNON. On a short-term basis, no, sir.

Mr. SMITH. And this period of commitment might be for several years?

Dr. SHANNON. Yes. At the present time, depending on the stability of the environment and the accomplishments of the individual, up to 5 years. Again I would emphasize the grants in general are made to institutions for the support of an individual who has demonstrated competence.

Mr. SMITH. That is why it is so vital to know who will be working on it.

Dr. SHANNON. He is responsible and the penalty he suffers is the loss of his grant.

CONTROLS TO PREVENT DUPLICATE EQUIPMENT PURCHASES

Mr. SMITH. How do you prevent duplicate equipment purchases?

Dr. SHANNON. Well, sir, I remember your comment back in 1961 relative to equipment. I think you made the statement then that, if Chevrolet can keep track of all its spare parts, we should be able to keep track of all our equipment. Was it not you who made that statement?

Mr. SMITH. Something like that.

Dr. SHANNON. Our best control on unnecessary duplication of equipment is in our project site visits. That is one method.

Our secondary control, which is broader and more extensive, is the system of review by one's peers. Very few of these people, if they are engaged in work that requires substantial equipment, are unknown by those who sit in judgment on the project. The applicant must list what

he has and what his requirements are and the new equipment that is requested is checkable. He makes an honest statement of what he has, an honest statement of what he believes he will need, and an honest statement of what he believes he will accomplish. It is on that basis that a grant is made, without his knowledge of the group that will examine his request, so that we feel there are automatic checks built in.

I do not think we can carry an inventory of all the scientific equipment in this Nation. There are varying rates of obsolescence, varying rates of breakdown, and varying rates of use. I think we have to use the methods I have indicated to you to assess the needs.

Mr. SMITH. Do you ever retrieve equipment from a grantee who no longer needs it and that a new grantee will need?

Dr. SHANNON. Very infrequently. We purposely reached this decision early in the program. We found that equipment purchases, or equipment in general, serve an extraordinarily useful purpose beyond the grant. From the start of our research grant program, except in unusual circumstances, the title to the equipment resides with the grantee, or rather with the institution.

What has sometimes happened—I know this to have been the case on several occasions—is that a man, who has been fully equipped in one institution, has moved to another institution and has requested a duplication of his equipment. In those cases, we have been able to negotiate with that institution so that he has been permitted to take his equipment with him. But these would usually be large equipment purchases under very substantial grants. Conventional equipment for the conventional projects are general purpose items that are usually used by others within the department or institution. We would be foolish not to encourage their use by anyone in the institution. At times, if a rather unusual piece of equipment is requested, one of the things that enters into a determination of whether the applicant will get it is whether in addition to meeting his general needs it will also be used by others.

Mr. SMITH. So you never have retrieved equipment?

Dr. SHANNON. Yes, but it is unusual.

Dr. SHERMAN. A large piece of very specialized equipment used for a particular line of research and not of a type where another investigator, or other investigators, in the same institution can make efficient use, could well be reclaimed by the Institute and used elsewhere.

Mr. SMITH. Since you do not retrive equipment why would not a grantee, if he had unused funds left at the end of the grant, use the unused portion of the grant to purchase equipment that he may want but that is not necessary to carry out the purpose of the grant?

Dr. SHERMAN. There is that tendency but we feel the system of checks and balances within the institutions will reduce that to a minimum. It is not a perfect system but it certainly is a vast improvement over what it was a decade ago.

DISPOSITION OF UNUSED PROJECT FUNDS

Mr. SMITH. How much unused money was returned last year?

Dr. SHERMAN. I am not sure of the exact figure. I would say some-

thing, overall, on the order of $5 million. There are unobligated funds. They are not returned to the Treasury.

Mr. SMITH. I am talking about unused project money.

Dr. SHERMAN. Unused in the sense that it was not used in the institution?

Mr. SMITH. The grantee did not use all the money he had available.

Dr. SHERMAN. I could not give you that figure off the top of my head. But funds are returned in a number of different ways, and simply to say that the investigator did not use it probably would not give a fair answer to your question.

Mr. SMITH. The fact is we are getting practically nothing in the return of unused project money, is that right?

Dr. SHERMAN. The return is in one sense unused but, in another sense, immediately reused because we apply it to the amount necessary to support the project the next year.

Mr. SMITH. Let us say it is the end of the project.

Dr. SHERMAN. I would say that we get something in the order of 8 percent of our research grant appropriation back at that time. This would be in the order of about $40 million, but we reuse it.

Mr. SMITH. For another grant?

Dr. SHERMAN. Yes.

QUALITY CRITERIA USED IN FUNDING RESEARCH PROJECTS

Mr. SMITH. On the basis of your own criteria for rating these grant projects, as more money has been available, naturally you moved into funding projects of lesser quality and the average quality of the projects has declined as more money has been available, naturally?

Dr. SHERMAN. No, sir. In the first place, you have to remember that during one period of time we turned back very substantial unobligated funds because we felt they could not be used profitably. One year I recall returning nearly $100 million. Even during the periods of time when we had these large balances, we required that large grants be separated out for independent action by the advisory councils.

Mr. SMITH. There is a quality level below which you would not go, but the more you fund, the lower quality level you have. Is that not mathematically correct?

Dr. SHANNON. If you consider that for several years the point to which we funded was reflected more in the amount of money we returned to the Treasury than in the amount of money we spent, you will see that the cutoff point was substantially above the minimal. At the present time we are funding about 35 or 40 percent of the grant applications. We are now at the level where we probably will not support, this year, much below the mean in the priority scale, so we are well away from the lower end of the scale.

I do not think this is good because it tends to exclude the young individual without a scientific reputation and the individual who has a wholly novel approach. The approval of an application is based on a consensus and, after all, novelty is not conducive to a ready consensus. Two or three years ago I traced the grant-approval experience of a number of outstanding investigators over a period of 15 years. These were people who had long research experience and were very productive.

The thing that distressed me was that the priorities that were given at various times varied very, very widely, though we were dealing with the same individuals in roughly the same fields. I reached the conclusion then that priorities are only very rough guides to relative excellence. They are the best we have. I wish we had better. A person who has a novel idea may have a low priority.

Mr. SMITH. To the extent you have already used the scientists and expert personnel available, funding some other projects would tend to rob some of those projects, would it not, so you must have a cutoff point somewhere?

Dr. SHANNON. Yes. We do it depending on the field or the Institute. Some of the Institutes feel that they can rate the relevance of the projects sufficiently well to shift priorities.

Mr. SMITH. Do you have a firm cutoff point on the quality level of projects?

Dr. SHANNON. Yes, sir. The firm cutoff point is whether it is approved or disapproved. But the dollars available cuts off those recommended for approval in many cases, at a much higher point.

I will be very glad to supply for the record the figures on this and our estimate of what will happen this year. The quality cutoff here is not our determination because the determining factor today is the fact that the funds we have in the 1967 budget will not cover all of the work that we feel is very high quality work.

Mr. SMITH. Are you saying that there are experts and scientists available to do more work than there is money to hire them?

Dr. SHANNON. Very definitely.

Mr. SMITH. How many grants do you allow one grantee to supervise?

Dr. SHANNON. It depends to some extent on the manner in which the department is run. I can recall that in one medical school a professor of biochemistry has all of his department's grants in his name—he is very responsible.

In most instances, grants are made to individual members of a department. There are some individuals who will get grants from NIH and from a private agency too, but our actions are taken with full knowledge of this, because the individual, when he makes his grant application, outlines specifically the support he is receiving from any other agency, at the time he makes the grant application, and he also indicates any proposed requests for funds in the same field, whether they have been made or not and before they have been considered, so this information is available to the reviewing group.

WOOLDRIDGE COMMITTEE RECOMMENDATIONS ON REDIRECTING RESEARCH

Mr. SMITH. The Wooldridge group made some recommendations about redirecting research. What do you have to say about that?

Dr. SHANNON. I will attempt to provide some information on that for the record.

(The information follows:)

In the "Report to the President, Biomedical Science and its Administration, A Study of the National Institutes of Health," the Administrative Panel which surveyed the NIH programs made the following recommendation:

"The Panel suggests, as a possible supplement, a convention that an investigator may immediately go ahead on a changed course if his institution approves, or perhaps if his institution, after being informed, fails to object; in either case NIH would be promptly informed and given a chance to veto the change, without retroactive effect, within a stated reasonable period."

The National Institutes of Health position regarding changes in scientific direction of research grant supported projects is as follows: Since statutes clearly place the responsibility for selection of projects on the Public Health Service, we continue to require that the investigator obtain PHS approval if he proposes to shift substantially the direction of the project. The language of present policy does, however, provide considerable latitude for making scientific changes in project operations without consultation of the PHS.

Present instructions to grantees, as presented in "Public Health Service Grants for Research Projects—Policy Statement" (PHS Publication No. 1301), are as follows:

"CHANGES IN RESEARCH PROTOCOL

"The permissible changes by the principal investigator in the approved project shall be limited to changes in methodology, approach, or other aspects of the project that would expedite achievement of the project's research objective, including changes that grow out of the approved project and serve the best scientific strategy. Whenever the grantee institution and the principal investigator are uncertain as to whether a change complies with these provisions, the question shall be referred to the awarding Institute or Division for a final determination."

WOOLDRIDGE PANEL'S RECOMMENDATION ON PROGRAM REVIEW

Mr. SMITH. That panel also recommended a regular review of the entire program in each discipline. Will the answer to this be included in your statement supplied for the record?

Dr. SHANNON. No, sir. I will give another answer to that.

It is our view, with reference to that recommendation, that it is an unreasonable recommendation. We have been through an experience of this sort during the past year in response to questions raised by the President. There has been a review of the research programs of all Institutes and a written analysis has been submitted to the President. We are convinced from this, and from other reviews, that this kind of detailed review of science activities cannot be updated on an annual basis.

Mr. SMITH. You are not trying to accomplish that objective, then?

Dr. SHANNON. No, sir. We plan to conduct, within PPBS, an analysis of our program, by program objective. We propose to use these analyses, together with our own staff studies, to review, in depth, two or three fields per year so that perhaps in a 3-year period we will have covered the whole field. We expect that our information system will be in sufficiently good shape by July, to give us machine-type analyses of on-going activities. That will be sort of a superficial examination of the total operation but this superficial examination will give us information on program emphasis and will give us a type of planning information we have not had before.

PRIMATE CENTERS

Mr. SMITH. You are asking for an increase for primate centers from $9 up to $10.5 million?

Dr. SHANNON. Yes.

Mr. SMITH. The justifications state these facilities are for resident and visiting scientists to conduct research. Who are they?

Dr. SHANNON. Anyone who can make arrangements with the center. A good many of the scientists are from areas other than the university that serve as the host. It depends on the facility.

Mr. SMITH. Are the centers available to the staff of profitmaking institutions or corporations?

Dr. SHANNON. That question has never come up. I think I would say "no" because I would not know how to manage it. If a profitmaking company asked me, I would want to know what they wanted to do and if other means could be found to do it. I think if a profitmaking institution made that request and if the proposed work was high quality work and fit in with what we needed, I might permit it, but I have not had the question before.

Mr. SMITH. None have asked?

Dr. SHANNON. No. Most of the large pharmaceutical companies have very good facilities themselves.

PATENT POLICY

Mr. SMITH. What are you doing to be assured, to the extent that you can be, that research done with public money when a discovery is made that is patentable results in a patent?

Dr. SHANNON. Well, sir; in the first place we have a regulation—we have instances where the regulation has not been abided by, but we believe that in general it is—that an invention report must be made at the time of discovery. Such an invention report goes to the Department for determination as to whether it is in the best interests of the Government to provide for patent coverage of this or to provide for protection of the public by prompt publication. In general they decide the latter.

I said that these regulations are not always abided by.

Very frequently a discovery turns out to have been important in retrospect, but at the time the discovery was made it did not seem particularly important and consequently it was not reported. I can give you some very good examples of that in our own laboratories in Bethesda.

We are doing a very substantial amount of work in the field of automation of chemistry. We are using hardware—component parts—derived from industry. Our people who have developed these new techniques did not realize that the system that emerged was a patentable entity.

In much the same way, they have modified many of the chemical techniques to permit automation. Again, a chemical technique that is novel and new and supplies information not therefore available is a patentable entity. They did not realize that.

In this field, happening right in our own shop, there is a substantial body of patentable information for which we are now just developing invention reports to call attention to the fact that these are patentable entities.

We feel the devices are sufficiently good now to warrant consideration for general patenting. When patented, they become marketable entities. The question was: Should one file an invention report on the marketable entity as devised by the scientist; and then what about all of the modifications of tests that have been developed?

This is a very good example of how, in the laboratory, the day-by-day modifications of work do not seem important, but in retrospect, when you look at them as a package, you realize that they should have been reported.

Mr. SMITH. If you do not get the patent, does someone else apply?

Dr. SHANNON. Not if it is published, sir. If it is in the public domain as a published bit of scientific knowledge, it is no longer patentable nor, indeed, will the Patent Office consider it. It is thrown out. I do not understand some of the new patent proposals that have been made.

Mr. SMITH. In the field of drugs and health research, the first-in and first-out proposal would result in the patenting by others of inventions paid for by the Government would it not?

Dr. SHANNON. We are looking at this now. I would rather not comment on it because there are certain aspects of it that trouble me.

Mr. SMITH. The question arises under the assumption that whatever is in the public domain will result in lower drug prices. I do not know if that is justified or not. Is there substantial evidence that patented items are costing more than the ones that the Government paid for and released to the public domain?

Dr. SHANNON. Mr. Smith, I do not know what the Department's position is on this, but I will just repeat what I told Senator McClellan about 2 years ago. There are many areas in medicine where the lack of limited exclusivity retards the development and marketing of an important product. While under our patent guidelines, at the present time, it is possible to give limited exclusivity to an individual concern to exploit an invention, it is not possible under our guidelines to encourage an individual to enter the field on the assumption that if anything is developed he will indeed have some period of exclusivity.

This obtains more rigidly for the medical area than for any of the other areas, and I think we do our Nation a disservice. I am not a patent expert, but I was in industry for 3 years and I know the value of patents. I know that when I was in industry we would not spend the large sums that are necessary for development into a product unless we were sure we would have some period of exclusivity. Given that period, we were willing to risk very substantial sums.

Mr. SMITH. To what extent, though, does the failure to have this information available to everybody retard some other invention or discovery? In other words, if it is patented by an individual, does not having this information available to some other research scientist retard discovery?

Dr. SHANNON. There are very few areas in our field where you find the thing that is so important in defense, so-called report literature that is not generally available. Report literature is important in the biomedical field in such areas as vaccine development, virology, and cancer chemotherapy. Consumers of that information are very knowledgeable of precisely where they can have access to that report literature in the Department of Commerce. These are largely the industrial concerns.

Without being able to be precise, I would say that probably as high as 98 percent of our information appears in the open literature. We do not have large bodies of information not generally available. Although much is made of the explosion of information and the diffi-

culty of finding it, I do not believe that that really obtains today. I think it is a hazard, if one looks forward 5 or 10 years. There are today very few developments that are relevant that are not very well known.

Mr. SMITH. I think you indicated—if I am misinterpreting, please say so before I proceed—I think you indicated that you did not believe that we were failing to patent very many discoveries that we paid for.

Dr. SHANNON. No. I said we are patenting very few of them, but by putting them in the public domain we prevent their appropriation by others.

Mr. SMITH. Let us put it another way, then: In other words, it might be a patentable item which you put in the public domain, but you may not patent it; is that correct?

Mr. CARDWELL. In other words, every time a report of invention is submitted, a determination is made by the Department as to whether it is a patentable item or not. From that point, the decision is made whether to publish.

Mr. SMITH. From the public benefit viewpoint, you believe it is equally as good?

Mr. CARDWELL. That is correct.

Mr. SMITH. I have been intrigued by the fact that although some of the companies have a very substantial number of Government grants and do very little on their own in terms of dollars, all the patents happen to have occurred on the few projects they financed and very few on the ones under NIH.

Dr. SHANNON. We make no grants to profitmaking organizations. The work we support there is by contract for quite specific purposes.

Mr. SMITH. I should have said "contract" where I said "grant."

Dr. SHANNON. Our support of industry generally is small as contrasted to their own support. Industry supports its own work to the extent of about $590 million. Our contract program, largely limited to allergy and infectious diseases and cancer, is about $70 million. So, quite apart from the substance of what we support——

Mr. SMITH. I am talking about basic research. What private companies are doing largely is taking knowledge that the Government paid for and using their money, as they properly should, to develop techniques to distribute, to market, and to get the product out. Is that not true?

Dr. SHANNON. I would not doubt that a good deal of fundamental research and fundamental knowledge discovered in medicine is applied by commercial concerns. They have to make the decision whether they are willing to take the developmental costs and whether there is sufficient uniqueness to it that they can develop some process that would give them a price advantage over their competitors. I am not aware of much in the way of new drugs or new devices where private industry has profited greatly by this device. Quite the contrary. I think the problem is that, as there is no incentive without exclusivity, some of the observations that are made are not being developed.

MANPOWER BUDGET

Mr. SMITH. It has been said that you are not proposing any big increases in fellowships, and so forth, but when one looks at the total amount of money under the total budget—you have some under the Health Professions Act and elsewhere—there is a very substantial increase, is there not?

Mr. CARDWELL. The emphasis in the Health Professions is on the training of manpower to deliver services, rather than research manpower.

Mr. FLOOD. That worried me. You are telling us you cannot set up regions because you do not have manpower. Yet you are cutting back on your training programs. How do you put that together?

Dr. SHANNON. These are for training of scientists rather than service personnel. When you talk about regional medical programs, you are talking about medical specialists for service-oriented programs.

I think there is some provision in other parts of the Public Health Service to enhance training grants. The main bottleneck in the shortage of personnel is that it will take a long time to develop new medical schools. The re-engineering of the function of physicians is, I think, the only immediate answer to the problem.

Mr. FLOOD. Mr. Hull.

Mr. HULL. No questions.

Mr. FLOOD. Mr. Casey.

Mr. CASEY. I do not believe I have any questions, Mr. Chairman.

Mr. FLOOD. This is the end of Dr. Shannon's overall testimony. As the chairman of this subcommittee I am certainly very pleased to have Dr. Shannon in his capacity as Director of NIH. I will consider myself fortunate, indeed, if as long as, by the grace of God and the electorate, I serve as chairman, he continues in his present capacity. It will be a great service to the committee and to the Congress and to the country.

As we have done every year for the last several years, we will place several overall tables and statements in the record at this point.

(The material referred to follows:)

HISTORY OF THE 1968 BUDGET

SUMMARY

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$767,307	−$45,721	$721,586	−$27,083	$694,503	−$50,014	$644,489
Fellowships	58,750	−3,759	54,991		54,991		54,991
Training	150,232		150,232		150,232	−10,626	139,606
Regional medical programs	197,000		197,000	−62,000	135,000	−75,600	59,400
Mental health staffing							
State control programs							
Total grants	1,173,289	−49,480	1,123,809	−89,083	1,034,726	−136,240	898,486
Direct operations:							
Laboratory and clinical research	93,951	−598	93,353	−6,815	86,538	−4,847	81,691
Collaborative research and development	125,323	−5,199	120,124	+4,022	124,146	−11,109	113,037
Biometry, epidemology, and field studies	10,114	−402	9,712	+609	10,321	−398	9,923
International research	4,373	+598	4,971	−905	4,066	−694	3,372
Computer research and technology	8,100	−2,536	5,564	−8	5,556	−881	4,675
Biologics standards	9,374	−94	9,280		9,280	−631	8,649
Training activities	1,165	−6	1,159	+2	1,161	−32	1,129
Professional and technical assistance	4,150	−595	3,555	−6	3,549	−581	2,968
Review and approval	22,692	−778	21,914	−1,203	20,711	−1,278	19,433
Program direction	9,689	−175	9,514	−457	9,057	−170	8,887
Total, direct operations	288,931	−9,785	279,146	−4,761	274,385	−20,621	253,764
Total obligations	1,462,220	−59,265	1,402,955	−93,844	1,309,111	−156,861	1,152,250

DIVISION OF BIOLOGICS STANDARDS

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Direct operations: Biologics standards	$9,374	−$94	$9,280		$9,280	−$631	$8,649
Total direct operations	9,374	−94	9,280		9,280	−631	8,649
Total obligations	9,374	−94	9,280		9,280	−631	8,649

NATIONAL CANCER INSTITUTE

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$96,693	−$7,378	$89,315	−$2,998	$86,317	−$3,000	$83,317
Fellowships	4,608	−282	4,326		4,326		4,326
Training	13,778		13,778		13,778	−2,428	11,350
Total	115,079	−7,660	107,419	−2,998	104,421	−5,428	98,993
Direct operations:							
Laboratory and clinical research	17,006	−195	16,811	−389	16,422	−357	16,065
Collaborative research and development	71,190	−2,603	68,587	−1,818	66,769	−3,784	62,985
Biometry, epidemiology, and field studies	1,422	−53	1,369	−33	1,336	+74	1,410
Review and approval	3,171	−168	3,003	−196	2,807	−219	2,588
Program direction	1,401	−10	1,391	−88	1,303	+12	1,315
Total direct operations	94,190	−3,029	91,161	−2,524	88,637	−4,274	84,363
Total obligations	209,269	−10,689	198,580	−5,522	193,058	−9,702	183,356

NATIONAL HEART INSTITUTE

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$141,435	−$12,086	$129,349	−$8,871	$120,478	−$13,850	$106,628
Fellowships	7,850	−411	7,439		7,439		7,439
Training	18,401		18,401		18,401	−705	17,696
Total grants	167,686	−12,497	155,189	−8,871	146,318	−14,555	131,763
Direct operations:							
Laboratory and clinical research	13,720	−85	13,635	−382	13,253	−118	13,135
Collaborative research and development	21,122	−1,163	19,959	+4,613	24,572	−7,046	17,526
Biometry, epidemiology, and field studies	1,810	−101	1,709	+404	2,113	−386	1,727
Training activities	296	−2	294		294	+1	295
Review and approval	3,298	−138	3,160	−177	2,983	−320	2,663
Program direction	847	+3	850	+2	852	−7	845
Total direct operations	41,093	−1,486	39,607	+4,460	44,067	−7,876	36,191
Total obligations	208,779	−13,983	194,796	−4,411	190,385	−22,431	167,954

NATIONAL INSTITUTE OF DENTAL RESEARCH

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$18,262	−$1,060	$17,202	−$73	$17,129	−$1,220	$15,909
Fellowships	2,212	−241	1,971		1,971		1,971
Training	5,660		5,660		5,660	−191	5,469
Total grants	26,134	−1,301	24,833	−73	24,760	−1,411	23,349
Direct operations:							
Laboratory and clinical research	4,797	+9	4,806	−118	4,688	−90	4,598
Collaborative research and development	1,267	−56	1,211	−240	971	−111	860
Biometry, epidemiology, and field studies	465		465		465	−30	435
Review and approval	717	−20	697	−34	663	−1	662
Program direction	371	+5	376	+3	379	+24	403
Total direct operations	7,617	−62	7,555	−389	7,166	−208	6,958
Total obligations	33,751	−1,363	32,388	−462	31,926	−6,619	30,307

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$109,088	−$1,517	$107,571	−$4,157	$103,414	−$7,110	$96,304
Fellowships	7,000	−409	6,591		6,591		6,591
Training	18,000		18,000		18,000	−2,294	15,706
Total grants	134,088	−1,926	132,162	−4,157	128,005	−9,404	118,601
Direct operations:							
Laboratory and clinical research	14,874	−70	14,804	−208	14,596	−263	14,333
Collaborative research and development	7,149	−707	6,442	+697	7,139	+597	7,736
Biometry, epidemiology, and field studies	684	−62	622	+62	684	+67	751
Review and approval	2,401	+23	2,424	−90	2,334	−177	2,157
Program direction	463	−28	435	−36	399	−23	376
Total direct operations	25,571	−844	24,727	+425	25,152	+201	25,353
Total obligations	159,659	−2,770	156,889	−3,732	153,157	−9,203	143,954

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$95,455	−$5,828	$89,627	−$573	$89,054	−$4,638	$84,416
Fellowships	4,050	−245	3,805		3,805		3,805
Training	19,177		19,177		19,177	−397	18,780
Total grants	118,682	−6,073	112,609	−573	112,036	−5,035	107,001
Direct operations:							
Laboratory and clinical research	10,983	−169	10,814	−504	10,310	−313	9,997
Collaborative research and development	5,880	−271	5,609	+669	6,278	−298	5,980
Biometry, epidemiology, and field studies	2,060	−100	1,960	+275	2,235	+70	2,305
Training activities	72		72		72		72
Review and approval	2,631	−58	2,573	−49	2,524	−135	2,389
Program direction	896	+7	903	+1	904	−15	889
Total direct operations	22,522	−591	21,931	+392	22,323	−691	21,632
Total obligations	141,204	−6,664	134,540	−181	134,359	−5,726	128,633

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$57,004	−$3,169	$53,835	−$577	$53,258	−$322	$52,936
Fellowships	4,770	−503	4,267		4,267		4,267
Training	9,650		9,650		9,650	−399	9,251
Total grants	71,424	−3,672	67,752	−577	67,175	−721	66,454
Direct operations:							
Laboratory and clinical research	14,620	−91	14,529	−322	14,207	−461	13,746
Collaborative research and development	11,238	−98	11,140	+329	11,469	−444	11,025
Biometry, epidemiology, and field studies	1,442	−9	1,433	−31	1,402	−46	1,356
Review and approval	1,477	−20	1,457	+17	1,474	+8	1,482
Program direction	353	+4	357	+2	359		359
Total direct operations	29,130	−214	28,916	−5	28,911	−943	27,968
Total obligations	100,554	−3,886	96,668	−582	96,086	−1,664	94,422

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$92,617	−$4,901	$87,716	−$3,325	$84,391	+$872	$85,263
Fellowships	22,310	−1,400	20,910		20,910		20,910
Training	49,372		49,372		49,372	−3,643	45,729
Total grants	164,299	−6,301	157,998	−3,325	154,673	−2,771	151,902
Direct operations:							
Collaborative research and development	3,809		3,809	−62	3,747	−200	3,547
Training activities	479	+2	481	+1	482	+2	484
Review and approval	3,431	−103	3,328	−156	3,172	−149	3,023
Program direction	1,549	−52	1,497	−86	1,411	−83	1,328
Total direct operations	9,268	−153	9,115	−303	8,812	−430	8,382
Total obligations	173,567	−6,454	167,113	−3,628	163,485	−3,201	160,284

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$54,311	−$3,137	$51,174	−$2,979	$48,195	−$5,264	$42,931
Fellowships	4,370	−268	4,102		4,102		4,102
Training	10,149		10,149		10,149	−387	9,762
Total grants	68,830	−3,405	65,425	−2,979	62,446	−5,651	56,795
Direct operations:							
Laboratory and clinical research	8,419	+3	8,422	−814	7,608	−1,866	5,742
Collaborative research and development	1,234	−71	1,163	−58	1,105	+282	1,387
Biometry, epidemiology, and field studies	2,231	−77	2,154	−68	2,086	−147	1,939
Training activities	133	−6	127		127	−36	91
Review and approval	2,117	−64	2,053	−116	1,937	−151	1,786
Program direction	988	−40	948	−46	902	−21	881
Total direct operations	15,122	−255	14,867	−1,102	13,765	−1,939	11,826
Total obligations	83,952	−3,660	80,292	−4,081	76,211	−7,590	68,621

REGIONAL MEDICAL PROGRAMS

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants: Regional medical programs	$197,000		$197,000	−$62,000	$135,000	−$75,600	$59,400
Total grants	197,000		197,000	−62,000	135,000	−75,600	59,400
Direct operations:							
Professional and technical assistance	4,150	−$595	3,555	−6	3,549	−581	2,968
Review and approval	1,147	−104	1,043	−154	889	−73	816
Program direction	1,229	−28	1,201	−39	1,162	−32	1,130
Total direct operations	6,526	−727	5,799	−199	5,600	−686	4,914
Total obligations	203,526	−727	202,799	−62,199	140,600	−76,286	64,314

DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$12,242		$12,242	−$1,821	$10,421		$10,421
Training	5,545		5,545		5,545		5,545
Total grants	17,787		17,787	−1,821	15,966		15,966
Direct operations:							
Research (AKA) laboratory and clinical research	9,532		9,532	−4,078	5,454	−$1,379	4,075
Review and approval	422		422	−66	356		356
Program direction	318		318	−100	218		218
Total direct operations	10,272		10,272	−4,244	6,028	−1,379	4,649
Total obligations	28,059		28,059	−6,065	21,994	−1,379	20,615

GENERAL RESEARCH AND SERVICES

[In thousands]

Obligations by activity	National Institutes of Health to Public Health Service	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	President's budget
Grants:							
Research	$90,200	−$6,645	$83,555	−$1,709	$81,846	−$15,482	$66,364
Fellowships	1,580		1,580		1,580		1,580
Training	500		500		500	−182	318
Total grants	92,280	−6,645	85,635	−1,709	83,926	−15,664	68,262
Direct operations:							
Collaborative research and development	2,434	−230	2,204	−108	2,096	−105	1,991
International research	4,373	+598	4,971	−905	4,066	−694	3,372
Computer research and technology	8,100	−2,536	5,564	−8	5,556	−881	4,675
Training activities	185		185	+1	186	+1	187
Review and approval	1,880	−126	1,754	−182	1,572	−61	1,511
Program direction	1,274	−36	1,238	−70	1,168	−25	1,143
Total direct operations	18,246	−2,330	15,916	−1,272	14,644	−1,765	12,879
Total obligations	110,526	−8,975	101,551	−2,981	98,570	−17,429	81,141

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			[1] 8,125,448		
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	15,425,000
1951	49,845,000	12,725,000		[3] 47,334,750	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 [5]	[7] 126,725,000			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			[8] 560,000,000		
1962	583,000,000			[9] 738,335,000		
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	1,231,764,000			1,306,983,000		
1968 [11]	1,173,250,000					

[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, Mont.
[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.

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, 1958–68

SUMMARY

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
Total, operating accounts:							
1958	$162,541,000	$155,292,000	$154,966,000	$154,966,000	$182,789,000	[1] $171,966,000	$171,020,000
1959	[2] 189,706,000	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	[3] 448,425,000
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	742,333,000	736,326,000	741,518,000	736,326,000	710,187,000
1965	[4] 861,055,000	[4] 832,277,000	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	----------
1968	1,402,955,000	1,309,111,000	1,152,250,000	----------	----------	----------	----------

[1] In addition, $466,000 was transferred from "Grants to States for public assistance."
[2] Subsequent to 1958 Senate allowance this amount was increased to $195,253,000.
[3] Includes $7,000,000 transferred to "Construction of mental health-neurology research facility."
[4] Includes $30,000,000 for "Special cancer research."

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.

BIOLOGICS STANDARDS

	Public Health Service 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	7,884,000	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	----------
1968	9,280,000	9,280,000	8,649,000	----------	----------	----------	----------

NATIONAL CANCER INSTITUTE

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$51,608,000	$47,314,000	$46,902,000	$46,902,000	$58,543,000	$56,402,000	$55,454,000
1959	53,943,000	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	----------
1968	198,580,000	193,058,000	183,356,000	----------	----------	----------	----------

[1] Includes $10,000,000 transferred from "Special cancer research" appropriations in 1966.

SPECIAL CANCER RESEARCH

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1965	$30,000,000	$30,000,000	----------	----------	$10,000,000	$10,000,000	$10,000,00

NOTE.—Transferred to "National Cancer Institute" appropriation in 1966.

NATIONAL HEART INSTITUTE

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$35,822,000	$33,815,000	$33,436,000	$33,436,000	$38,784,000	[1] $35,936,000	$35,973,000
1959	[2] 34,683,000	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	----------
1968	194,796,000	190,385,000	167,954,000	----------	----------	----------	----------

[1] In addition, $147,000 was transferred to this account from "Grants to States for public assistance."

[2] Subsequent to 1958 Senate allowance this amount was increased to $37,139,000.

NATIONAL INSTITUTE OF DENTAL RESEARCH

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$6,635,000	$6,532,000	$6,430,000	$6,430,000	$6,430,000	[1] $6,430,000	$6,466,000
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
1965	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	----------
1968	32,388,000	31,926,000	30,307,000	----------	----------	----------	----------

[1] In addition, $50,000 was transferred to this account from "Grants to States for public assistance."

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$18,027,000	$18,024,000	$17,885,000	$17,885,000	$23,548,000	[1] $20,385,000	$20,480,000
1959	[2] 20,319,000	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	
1968	156,889,000	153,157,000	143,954,000				

[1] In addition, $97,000 was transferred to this account from "Grants to States for public assistance."

[2] Subsequent to 1958 Senate allowance this amount was increased to $21,929,000.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$19,945,000	$19,041,000	$18,887,000	$18,887,000	$24,058,000	$21,387,000	$21,060,000
1959	[1] 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	[2] 55,348,000
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	
1968	134,540,000	134,359,000	128,633,000				

[1] Subsequent to 1958 Senate allowance this amount was increased to $22,259,000.

[2] Includes $7,000,000 transferred to "Construction of mental health-neurology research facility."

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$16,407,000	$16,405,000	$17,400,000	$17,400,000	$17,400,000	[1] $17,400,000	$17,506,000
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	----------
1968	96,668,000	96,086,000	94,422,000	----------	----------	----------	----------

[1] In addition, $114,000 was transferred to this account from "Grants to States for public assistance."

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

	Public Health Service 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	----------
1968	167,113,000	163,485,000	160,284,000	----------	----------	----------	----------

NOTE.—Included in the "General research and services, NIH" appropriation prior to 1966.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

	Public Health Service 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)	[1]($34,000,000)	$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	
1968	80,292,000	76,211,000	68,621,000				

[1] Congress authorized the transfer of $34,000,000 from other NIH appropriations to establish the National Institute of Child Health and Human Development.

REGIONAL MEDICAL PROGRAMS

	Public Health Service 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	
1968	202,799,000	140,600,000	64,314,000				

[1] Supplemental appropriation.

[2] Not considered by the House.

DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

	Public Health Service 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	
1968	28,059,000	21,994,000	20,615,000				

GENERAL RESEARCH AND SERVICES

	Public Health Service estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1958	$14,097,000	$14,161,000	$14,026,000	$14,026,000	$14,026,000	[1] $14,026,000	$14,081,000
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	177,357,000	168,321,000	163,146,000	162,390,000	164,190,000	164,190,000	163,502,000
1966 [2]	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	
1968	101,551,000	98,570,000	81,141,000				

[1] In addition, $58,000 was transferred to this account from "Grants to States for public assistance."

[2] Excludes the "National Institute of General Medical Sciences" established as a separate appropriation in 1966.

DESCRIPTION OF EACH NIH GRANT PROGRAM

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 expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions and (2) 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 estimates	447, 986, 000
1968 estimates	483, 606, 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 1967 program of about $600 million in regular and special research grant programs. This will support about 13,500 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 estimates	[1] 51,700,000
1968 estimates	[1] 61,700,000

[1] An amount for NIMH *is included* here (1967—$6,434,000; 1968—$5,667,000) inasmuch as the total is obligated through NIH.

3. Present stage of development

In 1967 general research support grants will provide support for 296 health professional schools, hospitals, research institutes, laboratories, centers and certain other nonprofit research organizations heavily engaged in health related research. In addition approximately 100 academic institutions other than health professional schools will be supported. Approximately eight 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 1968 President's budget continues this program with an increased level of support, including support for 310 institutions or organizations under the basic program, 115 biomedical sciences support grants to academic institutions and 22 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

1961 obligations	$1,734,000
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 estimates	2,541,000
1968 estimates	2,397,000

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, conferences, 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.

1961 obligations	$1,937,000
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 estimates	2,800,000
1968 estimates	2,800,000

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*
Johns 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 1968 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 administratively 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 1967 awards will have been made to approximately 92 general clinical research centers.

Seventy-six categorical center grants had been awarded by the close of fiscal year 1966. As with the general clinical research centers program, the categorical programs have yielded important scientific accomplishments.

4. Plans for the future

The 1968 President's budget will be directed toward providing continuing and supplemental support to the centers receiving awards in 1967.

FUNDING OF CLINICAL RESEARCH CENTERS PROGRAM

Research center grants and physical resource component of program project grants

[In thousands]

	Obligations, 1961	Obligations, 1962	Obligations, 1963	Obligations, 1964	Obligations, 1965	Obligations, 1966	Estimates, 1967	Estimates, 1968
Division of research facilities and resources	$8,000	$22,123	$17,374	$27,057	$26,906	$28,500	$28,463	$30,443
Child health					209	198	500	500
Cancer	4,199	805	4,437	4,849	4,898	7,283	(1)	(1)
Mental	509	700	781	1,604	1,379	1,292		
Heart	3,962	1,782	2,048	1,597	1,580	4,500	4,500	4,500
Dental					212	344	400	400
Arthritis		481	1,119	1,202	1,249	1,500	1,500	1,500
Allergy		500	237	852	949	881	1,100	1,100
Neurology	537	577	1,353	1,200	1,200	3,000	3,150	3,150
Total	17,207	26,968	27,349	38,361	38,582	47,498	39,613	41,593

[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. 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 estimates	10,850,000
1968 estimates	10,850,000

3. Present stage of development

Program plans for 1967 call for the continuation of support for 55 established resources, and the funding of approximately five new resources.

4. Plans for the future

The 1968 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 estimates	3,100,000
1968 estimates	5,100,000

3. Present stage of development

Plans call for the continuation of support for 26 facilities and the funding of approximately 15 additional resources.

4. Plans for the future

The 1968 President's budget will provide for grants to approximately 10 new resources over the 1967 level.

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

1960 obligations	$1,917,000
1961 obligations	7,000,000
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 estimates	9,000,000
1968 estimates	10,500,000

3. Present stage of development

This program calls for six regional and one national center, the latter committed to research on the primate itself. The initial awards for all seven centers provided two grants, one for total construction costs, and one for annual operating costs. The operating award is made each year after a detailed review of the

proposed budget by the Division. All seven centers are now complete and in full operation.

4. Plans for the future

The requested funds in the 1968 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 estimates	1,500,000
1968 estimates	1,500,000

3. Present stage of development

This program was initiated in 1966 at a level of $1,500,000. In 1967 approximately 35 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 1968. Greater selectivity in funding is anticipated in 1968 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 estimates	3,820,000
1968 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 the study was expanded to a total of 28 clinics. During 1967 the study is being expanded to a full complement of 50 clinics.

4. Plans for the future

With the enrollment of clinics nearing completion, the study will proceed during the next 3 years to enroll a cohort of approximately 8,400 patients and to follow them for a period of 5 years. It is expected that the study will be completed in 1974.

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 both research and research training in the 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 estimates	3,500,000
1968 estimates	3,500,000

3. Present stage of development

The program initiated in 1966 at a level of $1 million has provided for the development of one center at the University of Iowa, one at the University of North Carolina in Chapel Hill, and a center in clinical pharmacology at Emory University.

4. Plans for the future

The President's budget will provide continuing support for the three centers being developed and other large scale projects being initiated and developed.

LIFE ISLAND UNITS

1. Purpose of program

The program is designed to provide "protected environment" facilities wherein special therapy programs can be pursued on a research basis. A "life island" is a special bed in which a patient, whose host defenses against infection are deficient, can be isolated from the surrounding environment.

2. Funds

1966 obligations	$566,000
1967 estimates	600,000
1968 estimates	600,000

3. Present stage of development

Six active grants provide settings to study life island and reverse isolation programs such as laminar flow units.

4. Plans for the future

The funds provided in the President's budget will be utilized to continue research under the grants active in 1967.

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 estimates	$3,000,000
1968 estimates	3,000,000

3. Present stage of development

In fiscal year 1967, the first year for this program, applications have been approved for the establishment of three centers. It is expected that two other applications will be approved with starting dates in FY 1967.

4. Plans for the future

The President's budget provides continuing support for and expansion of this program in FY 1968.

ANESTHESIOLOGY AND DIAGNOSTIC RADIOLOGY CENTERS

1. Purpose of program

The purpose of the anesthesiology center program is to provide research and training for clinical and laboratory investigation related to teaching and patient care in anesthesiology.

The planned diagnostic radiology center will provide for research, development and evaluation of new techniques in diagnostic radiology to bring the fruits of biomedical engineering to improvement of X ray investigation and to develop new methods of visualization of tissues.

2. Funds

1967 estimates	$500,000
1968 estimates	1,000,000

3. Present stage of development

This initial year of the program provides for the development of one anesthesiology center and the development of a diagnostic radiology center.

4. Plans for the future

The amounts in the President's budget provide for the continuing support of the anesthesiology center and the development of a diagnostic radiology center.

RESEARCH AND TRAINING GRANT CENTERS

1. Purpose of program

The purpose of the environmental health sciences centers 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. Center 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 estimates	$2,500,000
1968 estimates	3,500,000

3. Present stage of development

The 1967 plans include the continued support of 6 ongoing programs and two new centers to be established.

4. Plans for the future

The increase of $1,000,000 in the President's budget support ongoing programs and provide for the activation of three or four additional centers.

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. The National Cancer Institute is also merging under this program title the programs it previously carried as Categorical Clinical Centers.

2. Funds

See the table below.

3. Present stage of development

In 1966 the Heart Institute initiated the development of cardiovascular centers with planning grants to four instiutions; support for three of these is continued in 1967 with the activation of seven additional planning grants. These

awards are for ongoing programs in cardiovascular research and training and are expected to compete for major operational center funds within the next several years. Cancer institute now supports 36 specialized research centers; the funds for 1967 will allow increased support for existing activities plus the inauguration of several new installations. Also included are planning grants which support cost incurred by institutions in the development of longterm plans for cancer research, training and clinical services. Neurology began the development of stroke centers with six planning grants in 1966; seven centers will be in the planning stage in 1967.

4. Plans for the future

Funds in the President's budget will provide for continued planning support to the 1967 awardee instiutions 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 four new grants in 1968. Some previously initiated grants called for higher starting costs with lesser operating funds in 1968 making possible the funding of these new grants. Neurology plans an increase of one center in 1968 making a total of 8 in the developmental stage.

	Obligations		
	Actual, 1966	Estimate	
		1967	1968
Heart	$342	$800	$800
Cancer	8,057	12,590	12,590
Neurology	800	800	800
Total	9,199	14,190	14,190

ENVIRONMENTAL HEALTH SCIENCE CENTERS

1. Purpose of program

The purpose of the environmental health sciences centers 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. Center 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 estimates	$2,500,000
1968 estimates	3,500,000

3. Present stage of development

The 1967 plans include the continued support of 6 ongoing programs and two new centers to be established.

4. Plans for the future

The increase of $1,000,000 in the President's budget support ongoing programs and provide for the activation of three or four additional centers.

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 data omits NIMH but includes 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 of 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 estimates	7,993,000	9,439,000	5,682,000	23,114,000
1968 estimates	7,833,000	10,149,000	6,690,000	24,672,000

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 estimate	1,250	1,337	545	3,132
1968 estimate	1,105	1,338	617	3,060

4. Present stage of development

The decrease shown in this program in 1967 is due primarily to the exclusion of the National Institute of Mental Health.

5. Plans for the future

The number of Predoctoral Fellowships supported in 1968 will be decreased in favor of increasing the number of students supported in established graduate training programs.

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
Obligations:		
1959	45	$345,000
1960	52	400,000
1961	92	700,000
1962	91	700,000
1963	172	1,198,000
1964	177	1,199,000
1965	184	1,177,000
1966	166	1,199,000
Estimates:		
1967	166	1,200,000
1968	170	1,380,000

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 1936, 41; 1964 and 1965, 42; 1966 through 1968, 43. In 1967, as in 1966, 166 fellows will be supported.

4. Plans for the future

In 1968 approximately 170 fellows will be supported. This is an increase of 4 over the number supported in 1967.

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 estimates	1,248	26,526,000
1968 estimates	1,336	28,939,000

3. Present stage of development

Approximately 1,248 fellows will be supported in 1967. This is the sum of 183 Research Career Awards, a decrease of 1 from the 1966 level, and 1,065 Research Career Development Awards, an increase of 140 over 1966.

4. Plans for the future

During 1968, about 1,336 career fellowships will be supported. This represents an increase of 96 Research Career Development Awards and a decrease of 9 Research Career Awards over the number supported in 1967.

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 estimates	134,492,000
1968 estimates	139,606,000

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 1967 about 2,592 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.

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 estimates	34,300,000
1968 estimates	85,314,000

3. Present stage of development

Current plans provide for planning grants, feasibility studies and grants for pilot projects as bases for further development of sound regional programs.

4. Plans for the future

The amounts in the President's budget provide for additional planning grants and feasibility studies but the major cost increase factor will be the support of new or additional phases of pilot projects.

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Alternate: Dr. Lyndon E. Lee, Jr. (112), Director, Surgical Service and Chief, Extra-Va Research, Department of Medicine and Surgery, Veterans Administration, Washington, D.C. 20420

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C. 20301

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Col. Robert J. Hall, MC, USA, chief, cardiology service, Walter Reed General Hospital, OSC Box 136, Washington, D.C. 20012

Alternate for—Dr. Shirley C. Fisk, deputy assistant secretary (health and medical), Office of Assistant Secretary for Manpower, Department of Defense, Washington, D.C.

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Dr. James A. Halstead, Associate Chief of Staff for Research, Veterans Administration Hospital, Washington, D.C. 20420
Alternate for—
Dr. H. Martin Engle, Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, Washington, D.C. 20420

Brig. Gen. Archie A. Hoffman, Commander, USAF Hospital Andrews, Andrews Air Force Base, Washington, D.C. 20331
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Dr. Abner Wolf (69), Professor of Neuropathology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, New York 10032
Dr. Warren V. Huber, Chief, Neurology Division, Psychiatry and Neurology Service, Veterans Administration, Washington, D.C. 20420.
Alternate for: Dr. H. Martin Engle, Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, Washington, D.C. 20420
Dr. Roy E. Clausen, Jr. (Col) (MC) USA, Office of the Surgeon General, Army, Main Navy Building, Room 2063A, Washington, D.C. 20315
Alternate for: Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of the Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C. 20301
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EX OFFICIO MEMBERS

Dr. William H. Stewart, (Chairman), Surgeon General, Public Health Service, 9000 Rockville Pike, Bethesda, Maryland 20014
Col. Herschel E. Griffin, M.C., USA, Chief, Division of Preventive Medicine, Office of the Surgeon General, Department of the Army, Washington, D.C. 20301
Alternate for—Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary for Manpower, Department of Defense, Washington, D.C. 20301
Dr. James H. Matthews, Chief, Clinical Research in Pulmonary Diseases, Department of Medicine and Surgery, Veterans Administration, Washington, D.C. 20420
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Dr. Benjamin B. Wells, assistant chief medical director for Research and Education in Medicine, Veterans Administration, Washington, D.C.
Alternate for: Dr. H. Martin Engle, chief medical director, Department of Medicine and Surgery, Veterans Administration, Washington, D.C.
Capt. Paul D. Doolan, MC, USN, Executive Officer, Naval Medical Research Institute, Bethesda, Maryland.
Alternate for: Dr. Shirley Fisk, Department of Defense, Washington, D.C.
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Mr. Mike Gorman (70), Executive Director, National Committee vs. Mental Illness, 1028 Connecticut Avenue, N.W., Washington, D.C. 20036
Mrs. Geraldine Joseph (67), 5 Red Cedar Lane, Minneapolis, Minnesota 55410
Dr. Paul V. Lemkau (68), Professor of Mental Hygiene, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205
Dr. Reginald S. Lourie (68), Director, Department of Psychiatry, Children's Hospital of the District of Columbia, Washington, D.C. 20009
Mr. Earle E. Morris, Jr. (69), State Senator and Vice President, The Pickens Bank, P. O. Box 97, Pickens, South Carolina 29671
Mr. J. Quigg Newton, Jr. (68), President, The Commonwealth Fund, 1 East 75th Street, New York, New York 10021
Dr. Charles R. Strother (67), Director, Mental Retardation and Child Development Center, University of Washington, Seattle, Washington 98105
Dr. Robert L. Stubblefield (70), Professor and Chairman, Department of Psychiatry, Southwestern Medical School, University of Texas, Dallas, Texas 75235
Dr. Louis J. West (69), Professor and Head, Department of Phychiatry, Neurology, and Behavioral Sciences, University of Oklahoma Medical Center, Oklahoma City, Oklahoma, 73104
Dr. Charles B. Wilkinson (70), Professor and Associate Chairman, Department of Psychiatry, Kansas City Division, School of Medicine, University of Missouri, 600 East 22nd Street, Kansas City, Missouri 64108
Dr. Robin M. Williams, Jr. (67), Professor of Sociology, Department of Sociology, Cornell University, Ithaca, New York 14850

EX OFFICIO MEMBERS

Dr. John J. Blasko, Director, Psychiatry, Neurology, and Psychology Service, Veterans Administration, Washington, D.C. 20420
Alternate for: Dr. H. Martin Engle, Chief Medical Director, Department of Medicine & Surgery, Veterans Administration, Washington, D.C. 20420
Capt. Ralph L. Christy, MC, USN, Head, Neuropsychiatry Branch, Bureau of Medicine and Surgery, Navy Department, Washington, D.C. 20390
Alternate for: Dr. Shirley C. Fisk, Deputy Asst. Secretary (Health & Medical), Office of Asst. Secretary for Manpower, Department of Defense, Washington, D.C. 20301
Dr. William H. Stewart (Chairman), Surgeon General, Public Health Service, 9000 Rockville Pike, Bethesda, Maryland 20014

MORTALITY, MORBIDITY, AND COST OF DISEASES

CANCER

Statistics of the annual number of deaths and total current number of disabilities caused by the major diseases dealt with in the National Cancer Institute.

I. Cancer deaths in 1965 (estimated data in provisional report of the National Center for Health Statistics, Division of Vital Statistics)

Buccal Cavity	6,840
Digestive system	94,460
Respiratory	51,580
Breast	26,770
Genital organs	41,000
Urinary organs	14,210
Leukemias	13,080
Lymphomas	14,950
Other sites	33,430
Total, all sites	296,320

II. Cancer disability in 1965 (estimated on the basis of data supplied by the National Cancer Institute and the National Center for Health Statistics)

(a) Estimated cases under treatment	904,000
(b) Estimated person-days of disability (these estimates have a large margin of error):	
Restricted activity	54,000,000
Sick in bed	32,000,000

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 neopalsms.

(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.

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 1965—preliminary report (Division of Vital Statistics, National Center for Health Statistics)

Category:	*Number*
Arteriosclerotic heart disease (includes coronary disease or "heart attacks")	556,000
Cerebrovascular lesions (includes strokes and other blood vessel diseases in the brain)	203,000
Hypertension	67,000
Non-rheumatic chronic endocarditis and other heart muscle degeneration	53,000
General arteriosclerosis	38,000
Rheumatic fever and rheumatic heart disease	16,000
Other cardiovascular diseases	56,000
Total	989,000

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 1965 to June 1966)

	Disability category	
	Restricted activity	Bed disability
Average annual number of disability-days (millions):		
Cardiovascular conditions	429	172
Heart conditions	202	83
High blood pressure [1]	68	21
Average number of persons (thousands): [2]		
Cardiovascular conditions	1,176	471
Heart conditions	555	228
High blood pressure [1]	185	57

[1] Without heart involvement.
[2] 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 $25.5 billion for the year 1963. This figure includes:

	Billion
Direct costs (hospital and medical services)	$3.1
Indirect costs (non-productivity):	
From illness during 1963	3.4
Discounted future earnings of persons who died in 1963	19.0

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.

DENTAL DISEASE

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

The high attack rate of dental diseases that begin early in life and affect almost the entire population of our country, constitutes, in the aggregate, an alarming degree of disability. Widespread failure of many people to obtain dental examinations that might lead to preventive care, the irreversible nature of many of the oral diseases, and the fact that they do not respond well to home remedies have resulted in a staggering backlog of need. A large-scale national survey concluded that the level of dental health of the American people is "shamefully low."

Most dental disability is the result of carious processes. Although tooth decay and resulting pain is frequently temporary, the total effect is a staggering national burden of absenteeism and lost productivity. In the United States today approximately 800 million cavities are presently in need of treatment.

Another major cause of disability is the complex of degenerative processes that affect the gums and areas surrounding the teeth. Signs of such periodontal disease can be detected in early every adult American. Periodontitis, sometimes called pyorrhea, is the chronic, destructive stage of the disease. Unless controlled, the process leads to deterioration of the very bone supporting the teeth. More than half of the people over 40 have lost one or more teeth because of periodontal disease; and more than 20 million adults have lost all of their teeth from this condition. In addition, periodontal infections can be the cause of life-threatening and disabling systemic disease. In one such critical area, heart patients—par-

ticularly those with rheumatic heart disease or implanted heart valves—require special treatment during periodontal and other treatment procedures to avoid disabling systemic involvement.

Another most serious dental-medical problem is malignancy with five percent of all cancers originating in the mouth. Even with the best of care, patients who survive may be disfigured and disabled. Physicians and dentists are allied in attempting to find and treat such cancers early enough to check them.

Dentistry is involved in many other categorical fields of medicine. For example, processes leading to loss of collagen and destruction of connective tissue in gums may hold clues to disabling and prevalent collagen diseases; and genetic flaws or other defects in perinatal development are reflected in cleft palate and malocclusions, by far the most common congenital malformations of the mouth and face. The former condition affects over a quarter of a million persons in the United States, some 6,000 infants being born each year with cleft lip, palate, or both.

3. Estimated annual cost to the Nation

The annual cost of dental care in the United States is about $3 billion, approximately 10 percent of the amount spent each year on health care of all types. However, less than 2 percent of health research expenditures are allotted to dental research. The National Health Survey estimated that in 1964 nearly 3 hundred million dental visits were made by persons in the civilian, noninstitutional population. In addition to man-hours lost from productive work during dental visits, a heavy burden is placed on the national economy because of time lost through distracting pain, sick leave, and crippling disabilities. The burden to individual families may be high: In severe cases of cleft palate, for example, surgical procedures, speech training and other care may cost the family up to $15,000 before the child's 18th year.

In the face of a severely limited number of dentists to cope with this staggering burden or oral health problems, the greatest need is for emphasis on preventive dentistry, based on research in the biomedical fields related to oral health.

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 1965 (Source: National Center for Health Statistics, PHS)

Category:	
Diabetes mellitus	33,170
Gastrointestinal diseases (ulcer of stomach and duodenum, cirrhosis of the liver, gastritis, duodenitis, enteritis, and colitis)	42,440
Total	75,610

II. Disabilities

(Source: Diabetes and Arthritis Program, Division of Chronic Diseases, PHS, 1966.)

Number of persons in U.S. reporting chronic activity limitation due to arthritis (excluding gout and bursitis) during 1961–63: 3,293,700.

III. Estimated annual economic cost to the Nation

(Source: Diabetes and Arthritis Program, Division of Chronic Diseases, PHS, 1966.)

Arthritis and rheumatism, $4 billion.

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 III gives some additional morbidity figures supplied by Vital Statistics.

TABLE I

Category	Morbidity 1965	Mortality 1964
I. Parasitic infections:		
Amebiasis	2,768	65
Malaria	147	3
Schistosomiasis	[1] 304	6
Trichinosis	199	1
Other parasitic infections	(2)	709
II. Bacterial diseases:		
Brucellosis	262	4
Cholera	0	0
Diphtheria	164	42
Leptospirosis	84	14
Meingococcal infections	3,040	750
Pertussis (whooping cough)	6,799	93
Salmonellosis (excluding typhoid)	17,161	62
Tularemia and leprosy	360	11
Septicemia and pyemia	(2)	2,389
Tetanus	300	179
Tuberculosis	[3] 50,874	8,403
Typhoid fever	454	14
Strep sore throat and scarlet fever	395,168	95
Syphilis, new cases	112,842	2,619
Gonorrhea, new cases	324,925	23
III. Rickettsial diseases: Typhus	309	24
IV. Viral diseases:		
Chicken pox	[4] 153,682	153
Encephalitis	2,703	1,036
Hepatitis	33,856	745
Herpes zoster	(2)	81
Influenza	(2)	1,687
Measles (rubeola)	261,904	421
Mumps	[5] 114,491	50
Mononucleosis	[6] 8,322	20
Poliomyelitis	72	132
Rubella	[7] 100,842	53
V. Allergic disorders:		
Asthma	(2)	4,441
All other	(2)	127
VI. Multiple or unspecified classifications:		
Bronchitis	(2)	5,410
Emphysema	(2)	15,796
Meningitis (except meningococcal and tuberculosis)	[8] 2,783	----------
Pneumonia	(2)	57,764
Respiratory infections (acute upper)	[9] 249,219	776
Other respiratory diseases	(2)	28,238

[1] Only 2 States reported.
[2] Not reported.
[3] 1964 figures.
[4] Only 40 States reported.
[5] Only 38 States reported.
[6] Only 30 States reported.
[7] Only 37 States reported.
[8] Only 41 States reported.
[9] Only 17 States reported.

Morbidity statistics taken from Morbidity and Mortality Weekly Report, Annual Supplement, 1965, Vol. 14, Oct. 14, 1966, Communicable Disease Center, Atlanta, Georgia.

Mortality statistics taken from Vital Statistics of the United States, 1964, Volume II–Mortality–Part A.

TABLE II.—*Cost to the Nation's populace, 1964*

Item	Acute condition group			
	Infectious and parasitic		Respiratory	
	Total	Rate per 100 persons	Total	Rate per 100 persons
Number of cases	51,886,000	27.5	219,355,000	116.4
Restricted activity ... days	217,191,000	115.3	680,818,000	361.3
Bed disability ... do	104,133,000	55.2	321,129,000	170.4
Work loss ... do	18,061,000	25.6	100,860,000	143.1
School loss ... do	57,737,000	138.9	98,947,000	129.9
Work loss ... costs	$374,626,839	$531	$2,092,069,153	$2,969

Definition of terms:

Restricted activity—a day when a person cuts down on his usual activities for the whole of the day because of an illness. Includes bed-disability, work-loss, and school-loss days.

Bed-disability—a day on which a person was kept in bed either all or most of the day because of an illness. Includes those work-loss or school-loss days actually spent in bed.

Work-loss—a day on which a person loses the entire day because of an illness. Computed for persons 17 years of age and over.

School-loss—a day on which a child loses the entire school day because of an illness. Computed for children 6 to 16 years of age.

Statistics taken from:

1. Vital and Health Statistics—Current Estimates United States—July 1964–June 1965; Series 10, No. 25, November 1965 (DHEW, PHS, National Center for Health Statistics, Washington, D.C.). Tables I through 8.
2. Department of Commerce, National Income Division, Personal Income Section, Average Income of Full-time Worker, 1964.

TABLE III.—*Number of conditions reported in health interviews in civilian non-institutional population of the United States, acute and chronic, for period July 1964–June 1965*

	Incidence of acute conditions	Prevalence of chronic conditions
Pulmonary tuberculosis		52,000
Tuberculosis, arrested or inactive		381,000
Strep sore throat and scarlet fever	5,272,000	
Measles	6,810,000	
Rubella	2,370,000	
Chicken pox	4,110,000	
Mumps	3,026,000	
Infectious hepatitis		94,000
"Virus" infections, ill defined	27,681,000	
Active rheumatic fever		86,000
Inactive rheumatic fever		217,000
Common cold	115,132,000	
Other acute upper respiratory infections	30,915,000	
Influenza with digestive manifestations	6,118,000	
Influenza, other	57,812,000	
Pneumonia other than primary atypical	2,255,000	
Chronic bronchitis		3,246,000
Acute bronchitis	3,750,000	

Source: Health Interview Statistics, National Center for Health Statistics.

NEUROLOGICAL DISABILITIES

INTRODUCTION

The number of people who suffer from disabling neurological or sensory disorders in the United States is unknown. Estimates vary from 6 to 12 percent of the total population and as much as 20 percent of hospital admissions relate to disorders of the brain. 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

Although 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 14.3 percent of the total United States deaths in 1964. The Neurological and Sensory Disease Study, Jefferson Medical College, Pennsylvania Department of Health, 1964, has shown 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, National Disease and Therapeutic Index, 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

Disability category	Mortality [1]	Estimated total cases [2]	Estimated annual cost of care [3]	Remarks
NEUROLOGICAL				
Cerebral palsy	1,272	600,000	$500,000,000	National Health Education Committee (NHEC) estimates ½ cases are under 21 years of age. United Cerebral Palsy estimates 10,000 babies born each year with cerebral palsy: approximately 2.3 per live births (1959).
Cerebrovascular diseases (strokes).	198,209	2,000,000	[4] 440,000,000	⅓ of patients with CV ("strokes") are wage earners under age 65 made unemployable by the residuals of a stroke (Source: NHEC and Presidents' Commission on Heart Disease, Cancer and Stroke, 1964).
Epilepsy	1,979	1,000,000–2,000,000	680,000,000	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 1962, a total of 14,246 patients with convulsive disorders were institutionalized in State and county mental hospitals, costing approximately $28,492,000 a year for care (NIMH).
Multiple sclerosis	1,429	250,000	200,000,000	Multiple sclerosis 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.
Amyotrophic lateral sclerosis.	1,147	[5] 5,000–10,000	10,000,000	Amyotrophic lateral sclerosis (ALS) occurs most often between ages 40 and 60: approximately ⅔ are men in the working force.
Muscular dystrophy, other muscle disease.	604	200,000	125,000,000	Nearly ⅔ of known muscular dystrophy patients in the United States are children between ages of 3 and 13 (Muscular Dystrophy Associations of America, Inc.).
Parkinson's disease (paralysis agitans).	2,876	500,000	400,000,000	Most patients are 50 years or older. The number of persons with Parkinsonism who die each year believed 5 times greater than figure shown, because Parkinsonism, 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 Fund).
Tumors of brain and other parts of nervous system.	9,382	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 5th decade, with males having a slightly higher incidence than females.
Spina bifida and meningocele.	1,372	----------	----------	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; yet mortality rate is reported at 1,372.[6]
Accident and injury to nervous system.	----------	----------	----------	Accident and injury frequently result in long-term disabling conditions of the nervous system.
Skull fractures and head injuries.	[7] 34,000	630,000	----------	No figures available on the number who suffer life-long 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, series 10, No. 8, April 1964).
Paraplegia and quadriplegia.	----------	60,000	----------	From Paraplegia Workshop, Nov. 4, 1966, at Bethesda, Md. (NINDB).

See footnotes at end of table.

Range and cost of major chronic neurological and sensory disorders—Continued

Disability category	Mortality [1]	Estimated total cases [2]	Estimated annual cost of care [3]	Remarks
SENSORY DISORDERS				
Eye disorders:				
Legally blind	--------	411,000	$600,000,000–$900,000,000	"New Vistas for the Blind," p. 7, HEW Indicators, October 1966. About half of total blind are not employed; an estimated 76.4 percent of legally blind population in the United States is 40 years and over. Over half of the 3,500,000 partially seeing are under age 65 (U.S. National Health Survey). Almost 1,000,000 of the 3,500,000 have severe visual impairment (U.S. National Health Survey). Almost 12,000,000 (estimated) children in the United States require eye care (National Society for the Prevention of Blindness).
Partially seeing	--------	3,500,000		
Hearing disorders:				
Totally deaf	--------	126,000	62,300,000	In October 1964, 32,256 pupils were enrolled in American schools and classes for the deaf, according to American Annals of the Deaf (January 1965) at an average institutional cost of $4,000 per year. Of the estimated 80,000 totally deaf adults, half are assumed to be fully disabled and half partially disabled. Deafness incidence rises rapidly with age.
Other hearing impairments.	--------	6,000,000	----------	Prevalence based on data collected during U.S. National Health Survey, 1959-61. Concerning activity limitation, the survey reports: "About 93 percent of persons with hearing impairments * * * have no limitation of any kind in their usual activities because of this type of impairment."
Speech impairments:				
Speech defects interfering with normal development.	--------	[9] 2,390,000	----------	Data collected by U.S. National Health Survey (National Center for Health Statistics) in household interviews during 1959-61 indicates ½ of all reported speech defects were among children under age 15. Note.—The 2 deficits, "hard of hearing" and "speech and hearing" frequently occur together, making it difficult, statistically, to separate these 2 categories of impairments.
Other degrees of speech impairment (includes some cases of aphasia due to strokes and similar cerebral disorders).	--------	1,098,000	----------	Average prevalence of cases is based on data collected by the National Center for Health Statistics. An estimated 15 to 20 percent of the school population is affected by other degrees of speech impairment.
Reading disability	--------	[10] 2,500,000–5,000,000	----------	In fall of 1966 there were 43,055,000 children in grades kindergarten through 12th grade in U.S. public schools, and an estimated 6,700,000 more in private schools.

[1] Figures indicate deaths from neurological ailments during 1964, as reported by U.S. National Vital Statistics Division, 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] $140,000,000 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, December 1964).

[5] ALS fact sheet, "Amyotrophic Lateral Sclerosis," NINDB.

[6] "Spinal Birth Defects, Hope Through Research," 1966.

[7] Caveness, William F., and Walker, E. A., editors: "Head Injury Conference Proceedings," J. B. Lippincott Co., 1966.

[8] For 1963, Federal, State, and local financial aid to 97,800 blind persons totaled $97,000,000.

[9] 5 percent of schoolchildren.

[10] 5 to 10 percent of all schoolchildren.

NOTE.—The commonly accepted estimate is that 10,000,000 to 20,000,000 Americans have 1 or more neurological handicaps; many have multiple handicaps.

MENTAL ILLNESS

Statistics on the total current number of mentally ill persons receiving psychiatric care by type of facility and estimated costs.

I. Estimated number of patients under care

More than 2.4 million Americans received care for mental illness during 1965 in a variety of hospitals, clinics, and other outpatient units. Not included in this total are persons treated by private psychiatrists or other mental health practitioners, or treated in nonpsychiatric mental health facilities, or patients in institutions for the mentally retarded. The 2.4 million persons represent the sum of all admissions (excluding transfers) during the year and resident patients at the beginning of the year; for outpatient psychiatric clinics the number on the rolls of the clinics plus admissions during the year. To the extent that psychiatric patients are discharged from such facilities as general hospitals to mental hospitals or to psychiatric clinics there is some duplication in the count of admissions in combining data. The 2.4 million persons were treated in the following types of facilities:

Number of patients receiving care

Type of facility	1965	1966
State and county mental hospitals	807,000	807,200
Veterans' Administration hospitals	133,000	140,000
Private mental hospitals	114,000	115,000
General hospitals with psychiatric facilities	412,000	429,000
Outpatient psychiatric clinics	950,000	1,085,000
Psychiatric day-night units	14,000	14,500
Total	2,430,000	2,590,700

II. Estimated cost of care

To Federal, state, and local governments for care of patients, fiscal year 1966, $2,354,181,000.

BIOLOGICS STANDARDS

ONCOGENICITY IN RELATION TO VACCINES

Studies of the relationship between certain viruses and the tumors they produce in experimental animals have constituted, as in prior years, 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 demonstrated capacity of simian virus 40 (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. Contributions of the DBS staff to the development of this subject began with the first demonstration of the ability of SV40 to produce subcutaneous sarcomas in newborn hamsters in 1961.

Although the relevance of tumors in newborn hamsters to the problems of human cancer has yet to be assessed, and the hamster tumor viruses at the present time pose only a hypothetical threat to the public health, there is no tendency to minimize the eventual significance of the research under way in this area, and the newborn hamster stands out clearly as the animal of choice for testing potentially oncogenic viruses of mammalian origin. The hamster test, in fact, has become a criterion to be invoked in appraising 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. Simian virus 40 (SV40) and adenovirus 12 have been studied in detail by Dr. Bernice E. 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.

Dr. Paul Gerber, investigating the relationship between SV40 and its cellular environment, has found that cell-free fluids from hamster tumors produced by SV40 usually fail to yield any infectious virus, but cells from the tumor, when seeded onto sensitive indicator cells, become foci of SV40 infection. These cells, said to be in a "virogenic state," can be induced to pass on the SV40 infection to adjacent sensitive cells with increased efficiency following exposure to ultraviolet irradiated, non-infectious Sendai virus. The mechanism responsible has not been elucidated, but the inductive effect of the non-viable Sendai virus upon the totally unrelated latent SV40 virus adds another dimension to the concept of latency of viral infection.

When SV40 and adenovirus 12 were injected simultaneously into newborn hamsters by Dr. Ruth L. Kirschstein and her associates, 63 to 80 percent of the animals developed, within 12 weeks, tumors which were histologically identified as produced by adenovirus 12. Most of the remaining animals after 16 to 28 weeks developed tumors characteristic of SV40. No new types of tumors resulted from the double infection, and there was no evidence that either virus had been altered in its course by the presence of the other.

Although independently tumorigenic, SV40 and the adenoviruses are known to be capable of combining forces in a sinister way to form a hybrid virus with mutual survival benefits for the two parent viruses. The hybrid of SV40 with adenovirus 7 has been found by Dr. Kirschstein, in collaboration with Drs. Alan S. Rabson and George T. O'Conor of the National Cancer Institute, to produce SV40-type brain tumors in newborn hamsters after intracerebral inoculation. This confirms that the hybrid virus contains that portion of the SV40 genome which carries the oncogenic message. The hybrid does not exhibit the infective behavior of SV40, however, and thus is believed to contain only a part of the SV40 genome.

Adenovirus 3 is another of the adenovirus group which appears to be capable of hybridizing with SV40. Dr. J. Anthony Morris, working in collaboration with Dr. Eddy, and a group of investigators in NIAID, has found two strains of adenovirus 3 which, having come into contact with SV40, have acquired the ability to produce SV40 tumor antigen in cell cultures and SV40-type tumors in newborn hamsters.

In a research contract supervised by Dr. Kirschstein and Dr. Amos E. Palmer, 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 its lifetime, this study, while intricate, difficult, expensive, and of minor academic interest, nevertheless is believed to be essential to maintain our confidence in the safety of the biological products licensed by DBS for human use.

In a separate 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 of 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, promises to become a vital part of the DBS armamentarium. It represents, so far as possible, an extension of the interests and concerns of DBS scientists for the safety of biological products.

RUBELLA VACCINE

Rubella (German measles) is one of the common viral communicable diseases of childhood. It is usually clinically benign. The major hazard of the rubella virus lies in the risk of its transmission to the fetus during early pregnancy, resulting in fetal abnormalities, known as teratogenesis. These rubella-induced defects include blindness, deafness, congenital heart disease, and brain involvement resulting in mental retardation.

Since the disease is less communicable than rubeola (common measles) and chickenpox, about 1 in 5 persons can expect to reach adulthood without having had rubella. Thus, a sizable percentage of women in their child-bearing years possess no protective antibodies against rubella, and if exposed during pregnancy, may give birth to deformed children.

Rubella was first linked with birth defects in 1941 by Dr. Norman Gregg, an Australian ophthalmologist, who traced an unprecedented number of cataracts in babies to an epidemic in 1940.

Methods for laboratory study of the agent did not become available until 1962 when two groups of investigators, one at the Harvard School of Public Health and the other at Walter Reed Army Institute of Research, simultaneously reported the propagation of the virus in cell cultures. The discovery, a result of experiments completed in late 1961 and early 1962, was achieved independently and by different methods by Drs. Thomas H. Weller and Franklin A. Neva, of Harvard, and by Drs. Paul D. Parkman, Edward L. Buescher, and Malcolm S. Artenstein of the Walter Reed Army Institute of Research.

Shortly thereafter, the impact of the nationwide epidemics (1964 and 1965), with an estimated 20,000 babies born with rubella-induced abnormalities, focused the public attention on the rubella problem and the need for a vaccine to prevent the disease.

Since that time, investigators in this country and abroad have attempted to develop immunizing preparations with both killed and live rubella virus. Both preparations, however, posed problems of considerable complexity.

There has been little progress in the development of a "killed" rubella virus vaccine. Although the rubella virus is readily inactivated, thus far no one has been able to prepare a completely inactivated virus preparation that retains sufficient antigenicity to evoke a protective antibody response in man.

Initial work by several research groups with live virus preparations were equally discouraging. Several tissue culture propagated rubella virus materials when inoculated into volunteers produced a rash disease and the infection spread to involve uninoculated persons.

As a result of the increasingly intensive study of rubella by a number of investigative groups, the Division, in 1964, established a comprehensive research program in order to facilitate the ultimate licensing and control testing of the hoped-for vaccine. Drs. Harry M. Meyer, Jr., and Paul D. Parkman, because of their arcknowledged expertise in viral immunology, were placed in charge of the program. In the course of two years of intensive study, they developed a rubella virus strain which meets the generally accepted requirements—that is, one that will produce a non-transmissible infection, yet confer long-term immunity.

Since earlier workers in the rubella field had ben hamstrung by a lack of assay methods which could be used to signal that their manipulations had actually modified the virus, the DBS workers first concentrated on the development of laboratory methods that could be employed to detect changes in the virus induced by protracted cell culture passage.

They subjected several rubella virus strains to repeated passage in primary African green monkey cell cultures. As the progressively higher virus passage levels were obtained, their biological characteristics were carefully studied. High-passage virus was found by *in vitro* techniques to be distinctly different from low-passage "virulent" virus. The high-passage material caused a rapid cytopathic effect and other distinctive changes in certain types of tissue cultures relatively unaffected by the "virulent" virus. Also, the high-passage virus induced the production of increased amounts of interferon when propagated in tissue cultures.

Of primary importance, however, was the finding that the high-passage virus of the 77th passage level (HPV–77 strain) when inoculated into rhesus monkeys, resulted in the development of immunity without viremia or spread to uninoculated contacts.

These laboratory observations clearly indicated that the HPV–77 rubella virus strain had been sufficiently modified by tissue culture passage to use in an experimental vaccine. The vaccine was prepared under the same rigorous standards and safety tests that apply to the production of the live attenuated vaccines for measles and poliomyelitis. The next step was a clinical trial of the vaccine.

Clinical trials of adequately tested rubella virus preparations offer little risk if done in such a way as to insure that pregnant women are not exposed to vaccinees or to persons infected by contact with vaccinees. These precautions can best be carried out in institutions where the population is less mobile than in the community-at-large and the movement of personnel is subject to administrative control.

The Arkansas Children's Colony, a State educational institution for mentally retarded children, met these requirements. The Colony is situated in a rural area near Conway, Arkansas, and the children live in cottages, thus making it possible to isolate small groups from outside contact for a number of weeks with no interruption in their training program.

It was here that the Meyer-Parkman team conducted the pilot studies with their experimental vaccine, working with the full cooperation of the Department of Pediatrics, University of Arkansas School of Medicine, and personnel of the Arkansas Children's Colony.

Sixteen girls, with the written consent of their partents, were selected for the study. All were rubella-susceptible. Eight were inoculated with the high passage virus preparation. The other eight served as controls. All lived in the same cottage in close contact with one another. None of the inoculated girls showed any sign of rash, or enlargement of the lymph nodes, or illness which could be attributed to the vaccine, yet all developed virus neutralizing antibodies indicative of immunity. None of the uninoculated became infected.

These results indicated that the HPV–77 rubella virus strain was attenuated and produced non-communicable, immunizing infections in recipients.

Drs. Meyer and Parkman immediately revealed their findings to senior scientists in several universities. In these consultations, all agreed that it was important to confirm these observations with the least possible delay by conducting a similar but more extensive trial.

The second study involved three cottages and 48 rubella-susceptible children. Twenty-six children were inoculated; 22 served as controls. The results of this trial completely confirmed the findings of the original pilot study and were promptly reported to the scientific community.

The DBS research team was honored in a special PHS awards ceremony for developing the first attenuated rubella virus strain, and for using this strain to produce an effective live rubella virus vaccine. Dr. Meyer was awarded the Meritorious Service Medal, one of the highest honors awarded by the Department to a member of the PHS Commissioned Corps, and Dr. Parkman the Service's comparable award for civil servants, the Superior Service Medal. The two pediatrician-virologists also received personal letters of congratulations from President Johnson.

In the ensuing months, Drs. Meyer and Parkman have conducted further clinical studies with their experimental vaccine. Also, several university groups have used the vaccine to confirm the original findings of the DBS investigators.

The HPV–77 strain has been made freely available to investigators, and a number of pharmaceutical manufacturers, both in the United States and abroad, are now engaged in further developmental research with this and other experimental rubella virus preparations.

The NIAID Vaccine Development Branch is presently engaged in studies with the HPV–77 virus strain. The DBS research group is working in close cooperation with them, and every effort is being made to speed the development of a rubella vaccine that can be licensed for commercial use. The continuing efforts of the DBS research team and of the Vaccine Development Branch of NIAID will make it possible for the DBS rubella research breakthrough to be carried into the large-scale studies necessary to achieve the final goal—eradication of rubella.

RUBELLA IMMUNITY TEST

The remarkable progress since 1961 in the study of the rubella virus, the disease and, this year, the experimental vaccines, makes it possible to predict that rubella and its associated birth defects can be brought under control. However,

comparable progress had not been made in the development of diagnostic techniques, *i.e.*, tests for antibodies and immunity.

Those engaged in rubella research were well aware of the limitations of the three available serologic procedures. The neutralization test, while providing the most reliable and useful information, is expensive, complicated and time-consuming. The flourescent antibody method is beset by similar problems and provides less reliable results. Thus, neither test is ideally suited to large-scale use in diagnostic laboratories. The third method, involving complement fixation (CF), though technically simple, is less useful since rubella patients frequently fail to develop detectable CF antibody. When CF antibody does appear, it is relatively transient, thus the method does not lend itself to determining immunity in adults or others who may have experienced rubella some years earlier. Also, the test has no value in live vaccine studies since attenuated rubella virus infections do not evoke a CF antibody response.

This year, Drs. Meyer and Parkman and their research team in the Laboratory of Viral Immunology, DBS, perfected a rubella antibody method for measuring rubella immunity. The advantages of their test are its simplicity, speed, sensitivity and reliability. In addition, it is capable of detecting immunity years after infection. None of the previous techniques of rubella antibody measurement possess all of these attributes, although each has had its own area of usefulness.

Known as the H–I test (hemagglutination-inhibition), the method employs the biological principle of hemagglutination or red blood cell clumping, used successfully in studies on influenza and other diseases. Dr. Meyer and his co-workers found that special preparations of rubella virus cause the red blood cells of newly hatched chicks to clump. When they added a sample of blood from a person immune to rubella, the antibodies in the immune blood inhibited clumping. Thus, the inhibition of agglutination demonstrates the presence of antibody and immunity.

There are a number of potential uses for the new test:

Physicians caring for expectant mothers exposed to rubella can rapidly ascertain if there is cause for concern or if their patients are immune and at no risk. With any of the previous tests, the distressing period of anxiety was prolonged for weeks.

Reliable laboratory confirmation of rubella infection will be readily obtainable. Clinically, rubella is difficult to diagnose because of other unrelated rash diseases, and because many cases of rubella fail to develop recognizable signs of infection. In those pregnant, precise diagnosis is essential.

Women could be tested prior to marriage so that those lacking immunity could seek protection when rubella vaccine eventually becomes commercially available.

The new technique also promises to speed the availability of rubella vaccines since the effectiveness of experimental, attenuated virus preparations being used in clinical trials can be judged with far greater rapidity.

These findings were reported only a few months ago but samples of the diagnostic reagent and descriptions of the methodology employed have already been distributed to scientists around the world. The Vaccine Development Board of the NIAID and the DBS group have conducted a special workshop to enable pharmaceutical manufacturers and others involved in vaccine research to learn and apply the new technique without delay. Similar materials have been given to the Communicable Disease Center of the USPHS to assist them in aiding diagnostic laboratories across the country. Since the new immunity test is so inexpensive and easy to perform, it is expected to become routinely available in hospitals, health departments and other laboratories within the next few months.

Thus, one more major milestone has been passed in the research effort to conquer rubella.

CHOLERA

For the past five years the worldwide incidence of cholera has continued to increase and has now reached pandemic proportions. Confined for many years largely to the Indo-Pakistan Sub-continent, cholera now poses significant threats to Western Pacific nations and crucial areas in Southeast Asia such as Viet Nam. Westward spread through the Middle East and Southern Russia in the past year now places it at the very doorstep of Europe.

Cholera vaccine continues to be the most widely used weapon in combating this disease, and studies by Drs. John C. Feeley and Margaret Pittman of the DBS Laboratory of Bacterial Products are directed toward providing assurance that

current vaccines are of adequate potency, and toward the development of improved vaccines. DBS investigators are continuing their cooperation with international organizations, such as the Pakistan-SEATO Cholera Research Laboratory and the World Health Organization, to determine if the present method of laboratory assay best reflects the protective activity of vaccines in man, as established by controlled field trials in cholera endemic areas. Results of these studies to date continue to indicate that, of the several methods tried, the prescribed mouse protection assay correlates best with protection of man. However, further studies are needed to establish this point with certainty.

Recently, attention has been re-focused on the possibility that the cholera vibrio produces the disease by elaboration of a toxin which induces diarrhea in the victim. The studies of DBS investigators and those in other laboratories indicate that most current vaccines, while moderately effective in prevention of the disease, do not specifically induce immunity against the toxin. This suggests the possibility that the vaccine can be enhanced in efficacy by including a toxoid made from the toxin. DBS studies, in cooperation with the NIH Cholera Advisory Committee and the U.S.-Japan Cooperative Medical Science Program, are now in progress on methods of production and testing of the toxin and toxoid, with the aim of developing a new vaccine, the efficacy of which will be determined in a controlled field trial in man.

INFLUENZA VACCINE

The only effective means of controlling epidemic influenza is by vaccination. Inactivated influenza vaccines have been used for nearly 25 years with variable success, due to the continuing antigenic shifts in the prevailing viruses and the relatively short immunity engendered by the vaccines.

Epidemic influenza is caused by members of a family of closely related but distinct viruses, the most important of which are designated influenza viruses A, A1, A2, and B. The properties of these viruses do not remain constant but change from time to time in unpredictable ways. Unlike vaccines against other virus diseases such as smallpox, yellow fever, and poliomyelitis which are caused by more stable viruses, the protection provided by influenza vaccines depends upon representation in the vaccine of current influenza virus strains. Thus the composition of influenza vaccine is always subject to change as changes in the antigenic make-up of prevalent epidemic strains occur and when new virus subtypes periodically appear.

While monovalent vaccines of the appropriate influenza subtype strains may be most useful during a pandemic, polyvalent vaccines containing both A and B type strains are employed for routine immunization. The addition of too many strains, however, may dilute the efficacy of the vaccine, so it is imperative to choose those that are most likely to be prevalent during the influenza season.

The DBS is constantly looking for any evidence of change in the antigenic composition of influenza viruses as these viruses are isolated from patients during various outbreaks.

Because of the high rate of influenza spread, epidemic intelligence of this disease must be world-wide. The DBS therefore seeks its information from all possible sources, including the World Health Organization Influenza Centers, the Influenza Center for the Americas, located at the PHS Communicable Disease Center, as well as the military services of the United States.

When it is apparent that a particular strain has changed to the point at which little or no protection will be provided by the current vaccines, as when a new strain or type emerges, a change in the formula of the vaccine is called for. This happened in 1957 when the first A2 strain emerged. Usually, the changes are of lesser degree, but are such as to call for periodic review. Experience has shown that this review is best carried out in the early winter when information concerning the agents responsible for current or recent epidemics of influenza, both in the Northern and Southern hemispheres, is available. Based on such review, as well as any necessary additional laboratory and clinical studies, a decision can be reached as to the optimal strain formula for the vaccine for use the following fall.

The outbreak in 1964 of a severe A2 influenza epidemic in the Western Caroline Islands provided NIH investigators with an unusual opportunity to study the antibody response to infection in a population previously unexposed to contemporary strains of types A and B influenza virus. The study was carried out by Drs. Paul Brown and Carleton Gajdusek of NINDB, and J. Anthony Morris of DBS. The epidemic involved 100 percent of the population at risk and caused high

morbidity on three isolated atolls with a mortality of 7 percent on the most severely affected atoll.

Carried by ship, the epidemic swept through the islands where almost no one had pre-epidemic neutralizing antibody to any of the 7 strains of A and B influenza virus. After the epidemic, the highest neutralizing antibody titers developed against the contemporary A2 virus; successively lower titers developed against the earlier A2 strains.

Several neighboring atolls in the Caroline Island group, constituting a population of nearly 1,000 people, escaped infection during the 1964 epidemic. Subsequently, these people were shown by serologic tests to be potentially susceptible to both type A and B influenza, and therefore offer an opportunity to evaluate in a population of all ages the antibody response to influenza virus vaccines made from several different virus strains.

BLOOD PRODUCTS

Plasma fractionation products

As a basis for more useful and specific assay procedures for blood clotting and clot lysis, it is necessary for the DBS to carry out research directed toward purification and characterization of the components of the clotting system and toward developing and understanding of the details of their chemical interactions.

Recent studies of Dr. David L. Aronson, Laboratory of Blood and Blood Products, included the preparation from human plasma of highly purified prothrombin, the precursor of the enzyme thrombin, which catalyzes the ultimate clotting of blood. Examination of this prothrombin showed that, despite its purity, it was heterogeneous. The "impurities" however were not other protein contaminants, but a number of different prothrombins, all of which could be converted to thrombin. Such a finding suggests that these prothrombins actually represent discrete steps in the conversion to thrombin.

For this reason the single major type of prothrombin was converted to thrombin. At intervals during the conversion, aliquots of the reaction mixture were withdrawn, the reaction was stopped, and the products were analyzed. It became apparent that the conversion process involved at least three steps with two prothrombin intermediates.

However, in view of the complex nature of the system, it is not certain whether all of these steps are obligatory. It became necessary to attempt the isolation from human plasma of thrombokinase, the enzyme which appears, from the work of others on bovine blood, to catalyze the activation of prothrombin. Very recent work by Dr. Aronson has resulted in a purified human thrombokinase preparation and has shown that the same conversion pathway (three steps, two intermediates) was followed when this purified catalyst was used. Current work is aimed at elucidating the characteristics of human thrombokinase and of reaction conditions (including co-factors) influencing its catalytic activity.

Stability of gamma globulin and albumin

Work in several laboratories has indicated that during storage gamma globulin may undergo degradation from its initial molecular weight of approximately 150,000 to products of one-third this size. Since proteins of the latter size may be excreted in the urine, there exists the concern that although after storage a gamma globulin preparation might show good antibody activity when tested *in vitro*, it could fail to offer the needed protection when used clinically.

To assess the extent of this degradation under normal storage conditions, samples from 50 lots of gamma globulin, manufactured by four different firms each using a different starting material or manufacturing process, were examined in the DBS Laboratory of Blood and Blood Products after storage at 5° C over a period of 11 years. Considerable variation in the extent of breakdown was seen. In the samples from two manufacturers, the amounts of degradation products increased regularly with time; in those of another there was little change. The fourth showed intermediate changes.

Since this degradation has been attributed to the presence of a small amount of the enzyme plasmin (fibrinolysin), occurring as a contaminant in gamma globulin preparations, studies on the effect of adding human plasmin to gamma globulin were carried out by Drs. Edward H. Mealey and John Finlayson, LBBP. They found that when gamma globulin plus plasmin was incubated for 112 hours at 50°C, none of the breakdown to low molecular weight material occurred. (The optimal temperature for degradation seemed to be 24°C, *i.e.*, room temperature.) This result is apparently due to inactivation of the enzyme by heating;

therefore, studies are under way to determine whether heating of gamma globulin can prevent breakdown during subsequent storage.

The interest of the DBS extends to the stability of other blood plasma proteins. Recently completed studies by Drs. Mealey and Finlayson involved the physical chemical examination of several types of human albumin preparations stored at three different temperatures. The results have shown that under proper storage conditions albumin can be relatively stable for a period of 10 years. High temperature, even as high as room temperature, is to be avoided, as is storage in the dry state. Stability is somewhat greater when the albumin is stored as a 5 percent solution than when stored as a 25 percent solution, regardless of the temperature. The source from which the albumin is prepared (liquid or ultraviolet-irradiated dried plasma) has a considerable effect on its stability.

The Department of Defense and the Public Health Service maintain emergency stockpiles of both gamma globulin and albumin. It is essential to have information on the stability of these stockpiled products so that realistic dating periods, appropriate methods for recovering or reworking outdated material, and improved methods for the preparation and storage of future products may be designated.

POISON IVY

Poison Ivy is a disease that is purely American since the plant grows only in the United States and adjacent areas of Canada. At least 50 percent of the population has some sensitivity to the plant, thus making it one of the most common afflictions. Statistics from California indicate that there are more than 4,000 cases of occupational poison ivy dermatitis reported each year.

The disease, a form of delayed contact sensitivity, cannot be induced in all animals. It has been claimed that rabbits and mice do not become sensitive but that dogs do. Attempts at DBS to induce poison ivy sensitivity in rhesus monkeys met with failure, but guinea pigs have been sensitized and acquire a disease pattern that resembles that observed in human beings.

The sap of the poison ivy plant contains an active ingredient known as urushiol. Since the sap permeates all parts of the plant, contact with any part of it may induce the disease.

The active material can be readily extracted by alcohol or ether. Extracts can then be administered either orally or parenterally in an attempt to prevent the disease from recurring. The efficacy of such extracts is not generally accepted, and data demonstrating such extracts are efficacious are almost nonexistent.

The composition of the extracts, as well as their method of preparation, has been examined extensively by Professor Charles R. Dawson at Columbia University under a DBS contract, in collaboration with Dr. Harold Baer at DBS. It has been found that, although extracts that induce poison-ivy-like symptoms are easy to prepare, they usually do not contain much, if any, of the active ingredient urushiol. If extracts are prepared from fresh plant leaves, urushiol can be shown to be present in abundant quantity, If the leaves are stored, the urushiol is altered, probably by enzymes in the plant or possibly by air oxidation. The altered urushiol still retains a measure of skin reactivity. Thus, one of the difficulties with the extracts used for therapy is that few, if any, of the products contain the naturally occurring sensitizing agent.

It is frequently recorded that poison ivy grows on the east coast and that poison oak inhabits the west coast. Some investigators have felt that the plants were identical. Isolation of urushiol by Professor Dawson from poison ivy and poison oak indicates, from preliminary observation, that identical material is contained in both plants. The evidence, therefore, is that a single name is adequate to describe both poison ivy and poison oak dermatitis.

CANCER

CAUSATION OF LEUKEMIA AND LYMPHOMA

Scientists believe that the time is approaching when at least one virus will be identified as a cause of leukemia or lymphoma in man. Research leading to this goal has been carried out at the National Cancer Institute and other institutions throughout the country cooperating in the Institute's Special Virus-Leukemia Program.

The Program involves research on identifying unknown viruses, producing large quantities of highly purified viruses, and verifying the cancer-causing properties of the viruses under study. Knowledge obtained in this research would make pos-

sible planning and conducting of field trials to evaluate control measures, and control of the diseases by routine preventive or other control measures.

Firm evidence of the presence of two different types of virus-like particles has been obtained in studies of human leukemia and lymphoma tissue. Herpes-like virus, similar in size and shape to herpes viruses, which cause fever sores or shingles in man, was reported in Burkitt's lymphoma cells for the first time in 1964 by Dr. Michael A. Epstein and his associates of the Middlesex Hospital Medical School, London. Burkitt's lymphoma is a type of cancer, related to leukemia, most frequently involving the jaw and seen primarily in Africa. "C" type virus particles, identical in structure with viruses known to cause leukemia in laboratory animals, have been recovered from patients with leukemia.

TISSUE CULTURE STUDIES

One of the most rapidly moving areas is that of producing large quantities of viruses isolated from leukemia and lymphoma patients. Large amounts are needed for the many studies that hopefully will lead to identification of one or more causative viruses and development of vaccines.

In the past year progress has been made in establishing tissue cultures of cells from patients with leukemia and Burkitt's lymphoma, a related type of cancer most frequently involving the jaw and seen primarily in Africa. More than three dozen lines of lymphoid cells from as many different patients have been established in culture.

One of the cell lines was established for the first time from a patient with acute myelogenous leukemia at Roswell Park Memorial Institute. Another first was growth of a cell line from a patient with chronic myelogenous leukemia in the laboratory of Dr. Robert A. Manaker, of the National Cancer Institute's Viral Biology Branch. Herpes-like virus was detected in both of these cultures. Some of the cells in the culture of chronic myelogenous leukemia cells also contained the Philadelphia chromosome, an abnormal chromosome characteristic of this disease.

In the laboratory of Dr. James T. Grace at Roswell Park Memorial Institute several human leukemia and lymphoma cell lines have been established from single cells. The fact that electron microscopic examination showed herpes-like virus to be present in a significant percentage of the cells in each of several clones suggested that the virus or its genetic material is present in all the cells of the original cell line.

Dr. George E. Moore and his colleagues at the same research institution reported the first success in establishing cell lines from white blood cells of individuals who were not leukemic. The cultures were grown from the cells of a normal donor and a patient with rheumatic fever. Since the white cells are those most often affected by the leukemic process, these cell lines, if they prove to be virus free, may become valuable systems in which to determine the infectivity of the herpes-like and "C" type particles found in leukemia and lymphoma tissue.

Sizable quantities of the herpes-like virus are being harvested from several of the Burkitt's lymphoma cell lines. In addition, preliminary evidence of a virus called Reovirus 3 (*R*espiratory, *E*nteric, *O*rphan), found in human lungs and intestines, has been detected in cells from a number of patients with Burkitt's lymphoma and attempts are being made to establish the virus in culture. "C" type virus particles have been detected in several of the newly established cultures. These particles are not at present obtainable in quantity from tissue cultures, but they can be recovered in moderate amounts by a technique of collecting large fractions of blood plasma from leukemia patients.

In laboratory studies, a culture of leukemic cells from the blood of a monkey with chronic myelogenous leukemia was established by Dr. Manaker. The disease had been induced by other National Cancer Institute scientists by inoculation with a chemical known to induce cancer in laboratory rats and mice. Dr. Victor Zeve, Viral Biology Branch, examined the culture with the electron microscope and found large quantities of herpes-like virus, similar to those found in the cells of leukemia and lymphoma patients.

In a related long-term tissue culture study by Dr. Matilda Benyesh-Melnick of Baylor University, similarities were found between animal leukemias known to be induced by viruses and acute leukemia and infectious mononucleosis of childhood. Over a period of several years, some of the cells, known as fibroblastic cells, in bone marrow cultures derived from children with these diseases underwent spontaneous "transformation" to cells resembling a type of immature white

blood cell found in the blood of children with acute leukemia. None of the cultures from children with various other disorders or from normal children showed such changes. The factors responsible for these changes are unknown.

Immunologic studies

Observation of virus particles with the electron microscope is only suggestive evidence of the presence of viruses. However, by the use of other methods, such as the immunofluorescent technique, it is possible to obtain additional evidence of the presence of viruses in human leukemic cells and blood plasma and in cultures of cells from patients with leukemia and lymphoma. In the test, antiserum prepared in rabbits against virus-like particles recovered from human leukemic blood plasma is combined with a fluorescent dye. A positive reaction of the antiserum, as indicated by fluorescence, with cells from a test culture, indicates that the cells contain an antigen ("foreign" substance) that may be, but has not yet been proved to be, virus associated. About half of the established cell lines showed such immunofluorescence. The percentage of fluorescent cells in a given culture corresponded approximately to that of cells showing virus particles with the electron microscope.

Dr. Mary A. Fink and her associates of the Institute's Viral Leukemia and Lymphoma Branch found that immunofluorescence of cells from leukemia patients is related to the stage of the disease. Antiserum prepared against human leukemic material in which virus particles were found reacted with the blood cells of approximately 70 percent of patients in the active phases of their disease, and in less than 30 percent of patients in remission. No reaction was observed in specimens from normal persons or patients with other diseases.

Human gamma globulin (the fraction of blood that contains antibodies) was demonstrated for the first time in continuous tissue culture cell lines of human lymphoid cells, including many derived from Burkitt's lymphoma. This finding by Dr. John L. Fahey, Chief of National Cancer Institute's Immunology Branch, suggests the possibility of mass producing in tissue culture the specific antibodies needed for protection against disease.

Chromosome studies

Efforts to understand the nature of leukemia and lymphoma have prompted many studies of the chromosomal constitution of leukemic cells. The chromosomes carry the hereditary factors, or genes, of an individual and are constant in number in every species.

The only consistent chromosomal abnormality ever found in studies of cancer cells has been the Philadelphia chromosome, which is present in a majority of patients with chronic myelogenous leukemia (CML) and is unaffected by treatment. In a recent study by scientists at the National Institute of Arthritis and Metabolic Diseases and National Cancer Institute investigators of the Medicine Branch, patients who lacked the Philadelphia chromosome were found to respond less well to drug treatment and die sooner than those with the abnormality. This difference suggests that CML in patients who lack the Philadelphia chromosome may be a distinct clinical entity.

Dr. Robert W. Miller, Chief of National Cancer Institute's Epidemiology Branch, reported that congenital defects occur together with leukemia more often than can be attributed to chance. Clues to causation may be found in studies of relationships among these conditions.

For example, an excess of congenital defects and leukemia occurred in Hiroshima following the atomic bomb explosion. Environmental agents suspected of causing cancer—radiation, chemicals such as benzene, and viruses—can produce long-lasting genetic abnormalities. In addition, abnormal chromosomes characterize certain genetic disorders associated with a high risk of leukemia. It has been observed that the development of leukemia may be related to chromosomal breakage, whether inherited or acquired, as by exposure to ionizing radiation.

There is strong suggestive evidence that other genetic diseases, which are characterized by immunologic deficiency, such as congenital agamma-globulinemia, carry a high risk of lymphoma. Preliminary clinical and experimental data suggest that "acquired" immunologic deficiency is a precursor of lymphoma. These inter-relationships indicate that chromosomal and immunological abnormalities are probably related to the origin of leukemia and lymphoma, rather than to conditions accompanying these diseases.

TREATMENT OF LEUKEMIA AND LYMPHOMA

The most important recent advance in leukemia therapy has been intensive treatment with combinations of drugs active against the acute leukemias. Many laboratory studies and a few clinical studies to date have indicated that high doses of combinations of drugs administered for short periods, alternately with rest periods, appear to be more effective than other dosage schedules in producing long-term survivals. The goal of such treatment is destruction of all leukemic cells with minimum toxicity to the patient.

In a study reported by Dr. Edward S. Henderson, National Cancer Institute's Medicine Branch, children with acute leukemia were treated with high doses of four anticancer drugs by a 15-month intermittent schedule. The patients were relieved of all symptoms and signs of their disease for initial periods twice as long as those previously reported in studies of combination drug therapy, and they did not become resistant to the drugs. According to recent data, most of the 35 patients achieved complete remission for an average duration of about 13 months. Remission was re-induced in a large percentage of these patients after their disease recurred, and the average total survival time at last report was projected at more than three years.

Other investigators are studying the effects of treatment with drugs in combination with radiation, or with total-body radiation. In a study by Dr. Phillip George and his colleagues at St. Jude Children's Research Hospital and the University of Tennessee, combination of five anticancer drugs and a dose of radiation to the patients' central nervous system to destroy "hidden" leukemic cells were administered. At the last report in November 1966, most of the 32 children had achieved complete remission lasting longer than 19 months. At that time the median survival time was estimated to be about 28 months.

Dr. Ralph E. Johnson, Chief of the National Cancer Institute's Radiation Branch, reported preliminary results of treating small groups of leukemia and lymphoma patients with total-body radiation administered daily in small doses over several weeks. Total-body radiation has been investigated from time to time over many years, but has generally not been given in fractionated doses. A small group of lymphosarcoma patients showed a significant decrease in tumor size following an initial course of radiation and suffered very little illness due to the radiation. One patient at the time of reporting had maintained complete remission for 14 months with monthly exposures of 10 to 20 roentgens (units of radiation delivered).

In another small group of patients with chronic lymphocytic leukemia, Dr. Johnson reported that high lymphocyte counts were markedly decreased following fractionated total-body radiation administered in small doses, and symptoms of the disease were much improved. The results of this study suggested that there may be a qualitative difference between the leukemic and nonleukemic lymphocytes in sensitivity to radiation. This conclusion is based on the finding that in a control group of nonleukemic patients the lymphocyte counts which had not been elevated before radiation were hardly affected by the treatment.

Success in treating Hodgkin's disease, a type of lymphoma affecting the lymph glands and other infection-fighting tissues, is one of the most encouraging recent achievements in cancer therapy. Results of studies reported by scientists in several countries show that if the disease is discovered when it is localized and treated with intensive doses of X-ray, it can be completely controlled in nearly half of the patients for 15 years or more. Such patients can be regarded as cured.

Studies by Dr. Henry S. Kaplan at Stanford University and others have shown that the destructive dose for malignant cells in Hodgkin's disease is about 3,500 to 4,000 rads (units of radiation absorbed by tissue). Studies by Dr. Kaplan and others, which have shown that the disease spreads to adjacent lymph nodes in an orderly progression, have led to adoption of procedures for treating nodes in the immediate area of known disease with X-ray to ensure destruction of all malignant cells.

Dr. Johnson reported recently the use of radiation therapy in advanced Hodgkin's disease in which multiple lymph node areas were involved. Using carefully designed treatment schedules, he has administered high doses of radiation to many lymph node areas known to contain the tumor. Complete remissions have been observed in a majority of patients and undesirable side effects of such extensive irradiation have been tolerated satisfactorily.

Many studies are in progress to yield information on the action of chemotherapeutic agents on cells in the hope that a better understanding of the effects of drugs will lead to improved techniques for treating malignant disease. Preliminary studies suggested, for example, that rapidly multiplying mouse lymphoma cells in culture were several times more sensitive to an anticancer drug, 5-fluorouracil, than the normal bone marrow cells. If the differences in sensitivity to drug action are found to be related to certain stages in the life span of cells, then techniques of administering drugs to patients may be developed to capitalize on the vulnerable periods in the life of leukemic cells.

Other studies are emphasizing improvement in drugs. Cytosine arabinoside represents a new class of compounds of interest because it is active in early clinical studies against the acute leukemias in children and adults. Until now drugs have been relatively ineffective against the type of acute leukemia that occurs in adults, while five drugs have been found useful against acute leukemia in children. Another property of interest to clinicians is that the drug can be given in large doses, which are effective quickly, and then is rapidly eliminated from the body.

VIRAL CAUSATION OF SOLID TUMORS

Research on a possible viral cause of human solid tumors, such as those that occur in the lung, breast, or stomach, has been stimulated by the discovery of numerous virus-induced tumors in animals. In contrast to the leukemia-inducing viruses, which contain RNA (ribonucleic acid), many viruses that cause solid tumors in animals are of the DNA (deoxyridbonucleic acid) type. This difference in type of viral nucleic acid adds a new element to the problem of implicating DNA viruses in the causation of cancer. RNA viruses can be recovered from leukemic blood and tissue, but DNA viruses disappear from the tumor cell and cannot be recovered from tumors. Much of the research effort to date has been devoted to developing techniques for identifying DNA viruses in solid tumors.

Laboratory studies have shown that DNA viruses leave behind the information for the cell to synthesize a distinctive antigen, or "foreign" substance, that appears in the tumor cell after virus infection. Such antigens have been designated "T" (for tumor) antigens, and can be detected by their reaction with specific antibodies found in the blood serum of the host. Recent research has revealed the presence of "T" antigens in cells of tumors in hamsters and other rodents induced by human adenoviruses, which cause respiratory disease. Another DNA virus detected by its "T" antigen is SV40, which was isolated from tissues of the Indian monkey in which it apparently does no harm, but induces tumors in young hamsters.

Means of detecting antigens left behind by viruses may lead to the discovery of human cancer-causing viruses. Large-scale studies are in progress to examine blood serums of large numbers of cancer patients and normal controls for the presence of antibodies to DNA viruses.

Another clue to the presence of DNA viruses has come from the discovery that they may combine with other viruses to form hybrids. For example, a virus was discovered that appeared to be a hybrid between a human virus, adenovirus type 7, and SV40, present as a passenger in monkey kidney cells in which the adenovirus was being grown for vaccine production. The hybrid virus, which caused tumors in newborn hamsters, was believed to consist of a core of SV40 nucleic acid, alone or in combination with adenovirus 7 nucleic acid, wrapped in the protective protein coat of the adenovirus.

The concept of virus partnerships has implications for human cancer in addition to its possible usefulness in detecting DNA viruses. If hybridization of viruses is found to be a general phenomenon, it might suggest ways in which a relatively harmless virus could conceivably combine with another virus to become a highly malignant one.

A study by Dr. Alan Rabson and his associates in the National Cancer Institute's Pathologic Anatomy Branch has suggested that SV40 can form a hybrid with herpes simplex virus (a cause of cold sores). When monkey kidney cells growing in culture were inoculated with SV40 and about 24 hours later with herpes simplex virus, 5 percent of the cells contained both viruses within the same nucleus.

It is believed that DNA viruses may integrate their genetic material with that of the host cell and direct the cell to produce new viral materials. Results of a study reported in the past year showed that the RNA produced in adenovirus-

infected human cancer cells in culture consisted of an increasing amount of viral messenger RNA and a constant fraction of host cell messenger RNA. (Messenger RNA carries genetic information from one part of the cell to another where it acts as a template for formation of proteins.) These results also indicated that the infected host cell continued to produce its own RNA. The study was conducted by Dr. James A. Rose, National Institute of Allergy and Infectious Diseases, and scientists of the Metabolism Branch of the National Cancer Institute.

Another phenomenon showing the effect of combination of viruses is represented by the "helper" action of a mouse leukemia virus in completing a defective solid tumor-inducing RNA virus to form a fully infectious particle. Dr. Robert J. Huebner, National Institute of Allergy and Infectious Diseases, recently reported results of such a study. A mouse virus that induced solid tumors (sarcomas) in newborn hamsters could not be detected in the tumor tissue or recovered from it. Furthermore, extracts of the tumors did not cause new tumors when inoculated into newborn hamsters and did not induce foci of infection in tissue cultures. This indicated that infectious virus was absent from the extracts. However, when the hamster tumor cells were grown with mouse embryo cells and the mixed culture inoculated with mouse leukemia virus, focus-forming and tumor-inducing viruses were readily recovered. Preliminary studies indicated that the focus-forming viruses thus recovered had the outer-coat antigens of the "helper" virus and thus represented a newly created type of the sarcoma virus.

In the development of the breast tumor of mice, a well known animal cancer, three factors are involved: cancer-causing virus (the mammary tumor agent), genetic susceptibility, and hormonal stimulation. Dr. Vernon Riley at Sloan-Kettering Institute for Cancer Research showed that infection with LDH virus is a protective factor. LDH virus is widely distributed in mouse colonies but does not cause any known disease. It can be identified by the fact that it increases the activity of lactate dehydrogenase and other enzymes in the blood plasma. Mice infected with LDH virus had a significantly lower incidence of breast cancer, and developed such tumors later, than control mice not infected with the virus.

Research on DNA viruses is a rapidly expanding program of the National Cancer Institute. An important segment of the research is conducted by the National Institute of Allergy and Infectious Diseases. Other key studies are being carried out at research institutions and medical schools in this country and abroad, all aimed ultimately at evaluating the role of DNA viruses in the causation of human cancer.

TREATING SOLID TUMORS

A number of studies reported in the past year showed encouraging progress in the treatment of tumors in children. Dr. Sidney Farber, Director of Research, Children's Cancer Research Foundation, Boston, reviewed the results of long-term studies of treatment of Wilms' tumor, a cancer of the kidney in children, using a combination of an antibiotic, actinomycin D, surgery, and radiation. Almost all of a group of 53 children without widespread disease survived at least two years (in this disease almost always equivalent to cure) and some at the time of reporting had survived almost 10 years. Of 31 children whose disease had already spread to the lungs, an apparent cure rate of nearly 60 percent was achieved. Similar findings were reported in a group of 34 patients studied by Dr. Dale G. Johnson and his colleagues at the Children's Hospital of Philadelphia. Both groups have concluded that Wilms' tumor treated by surgery, radiation, and actinomycin D should be cured in most instances.

Dr. Wataru W. Sutow and his associates at the M.D. Anderson Hospital and Tumor Institute, Houston, Texas, reported that about one-third of a small group of children with cancers of the soft tissues, most cancer of the muscle cells, responded temporarily to therapy with vincristine, a drug derived from the periwinkle plant. One child was free of tumor two years after conclusion of the therapy.

To treat a variety of solid childhood tumors, concurrent chemotherapy with vincristine and actinomycin D was used by Dr. David H. James and his associates of St. Jude Children's Research Hospital and the University of Tennessee. Almost all of a group of 18 children with inoperable tumors showed some response lasting from 1 to 28 months. In two children, radiation following response to chemotherapy brought about further tumor regression, making surgery possible. The two drugs were used without severe toxicity, and with a possible additive antitumor effect.

Retinoblastoma, a malignant tumor of the eye, usually is found in children under the age of four, and one-third of the cases involve both eyes. It occurs once in approximately 23,000 births and is considered to be a congenital tumor. The aim of treatment is to save not only the life of the child, but also vision in at least one eye.

Dr. George A. Hyman and his associates at the Columbia University College of Physicians and Surgeons reported on 250 children with retinoblastoma affecting both eyes and with an outlook ranging from very favorable to very unfavorable. After treatment with a drug, triethylene melamine (TEM) prior to and following radiotherapy, the children had responses ranging from "useful vision and cure rate" of 85 to 22 percent. In another report by Drs. Algernon B. Reese and Robert M. Ellsworth of the same hospital, the dramatic effect of TEM on retinoblastoma was confirmed. These investigators suggested the occurrence of an additive effect in the action of combination radiation and drug therapy.

Reports on solid tumors affecting adults included an evaluation of treatment of a relatively rare type, cancer of the adrenal gland, first reported responsive to a drug, ortho,para' DDD, by the late Dr. Delbert M. Bergenstal and his associates of the National Cancer Institute. The drug, called o,p' DDD for short, whose production was sponsored by the Institute, is related to the insecticide DDT. Results of treatment with o,p' DDD evaluated by Drs. Adolph M. Hutter [1] and Donald E. Kayhoe [2] of the Institute's Chemotherapy Area, indicated that more than one-third of a group of 59 patients with evaluable, measurable disease had objective remission of their cancer lasting an average of about seven months after treatment.

Treatment of inoperable lung cancer with a combination of radiation and a drug, 5-FU (5-fluorouracil), was reported by Dr. Fred J. Ansfield and his associates at the University Hospitals, Madison, Wisconsin. A small group of 13 patients so treated had an average survival of almost two years at the time of reporting, and three were living more than five years. A similar group of 13 patients receiving radiation alone had an average survival of six months; one patient survived 14 months.

In another study, a small group of patients with far advanced reticulum cell sarcoma, related to the lymphomas and arising most frequently in lymph nodes, improved dramatically when given small doses of vincristine over a long period, despite the fact that these patients were previously resistant to other forms of therapy. Dr. William J. Yount and his associates at the United States Public Health Service Hospital, Boston, reported that signs of the tumors completely disappeared in 3 out of 9 patients, and regression was almost complete in 3 others. Remissions in these patients lasted 3 to 17 months.

Recent results show that some forms of cancer of the testis, often unresponsive to surgery and radiation treatment, are responsive to drugs. Dr. David A. Karnofsky reported that among 150 patients with advanced testicular cancer treated at the Memorial Sloan-Kettering Cancer Center, New York, with a combination of three well known drugs—actinomycin D, methotrexate, and chlorambucil—11 achieved long remissions. Nearly half of these patients survived free of disease longer than 10 years.

SMOKING AND LUNG CANCER

The problem of smoking as the principal cause of lung cancer continues to be a major source of concern to the National Cancer Institute. In the past year, several large statistical studies added new data to the evidence of the smoking and lung cancer relationship. In one, results were published on a study of 250,000 white male United States veterans that was begun in 1954 by the National Cancer Institute in cooperation with the Veterans Administration. The findings showed that cigarette smokers had a higher death rate than nonsmokers for lung cancer and almost every other disease. In one age group, 11 times as many smokers as nonsmokers died of lung cancer, and 12 times as many died of emphysema, also a lung disease.

Studies have shown that, among lung cancer patients, women have a survival advantage over men. Survival rates are lower among all patients with epidermoid carcinoma, the most common type of lung cancer in men, than among patients with adenocarcinomas, which occur more frequently in women. Dr. Roger R. Connelly and his associates of the National Cancer Institute's Biometry Branch

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[1] Now of the University of Rochester School of Medicine, Rochester, New York.
[2] Now of the National Institute of Allergy and Infectious Diseases.

reported on a study of survival of about 500 women and an equal number of men who had been operated on for lung cancer. Adenocarcinomas and alveolar cell tumors occurred about three times more frequently in women than in men. Yet, among patients of both sexes with these types of tumors, survival rates were substantially higher for women; on the other hand, among patients with epidermoid carcinoma survival rates in men and women were about the same. Other factors including extent of disease and amount of surgery performed, were also linked to the more favorable outlook for women, but part of their survival advantage remains unexplained.

Although no exact duplicate human lung cancer is known in laboratory animals, a new technique that induces in rats an epidermoid cancer of the lung similar to the human type has been devised by Dr. Mearl F. Stanton, National Cancer Institute's Laboratory of Pathology. A carcinogen is incorporated into a beeswax pellet and inserted into the lung tissue of the rat. The technique is useful for testing substances suspected of being carcinogenic (cancer-causing) in humans, and has shown that formation of keratinizing cysts in the rat indicates a potentially carcinogenic substance.

MAMMOGRAPHY-X-RAY EXAMINATION OF THE BREAST

Breast cancer, the most common single form of malignant disease in women in the United States, poses substantially the same threat to life that it did 30 years ago. Since many studies have emphasized the fact that breast cancer patients have a better chance of survival if the disease is diagnosed when the tumor is small, research has been focusing on new ways to find suspicious masses in breast tissue before they are large enough to be felt by a patient or her phyician.

Although various studies have yielded somewhat different results, reports thus far from a large-scale study supported by the National Cancer Institute have indicated that mammography, or examination of the breasts by X-ray, is revealing cancers not detectable by ordinary means. The X-ray examinations are being given by the Health Insurance Plan of Greater New York to 30,000 apparently healthy women between the ages of 40 and 64 to determine whether early detection, which will permit prompt treatment, will result in increased survival of breast cancer patients. Results of initial examination of 19,500 women seen through May 1, 1966 revealed a rate of detection of 2.50 cancers per 1,000 women. In the control group of women who did not have the X-ray examination the rate of detection was 1.53, which is close to the rate observed in the general population of women of comparable age in the United States. It is, however, too early to determine the effect of early detection on the survival of patients with breast cancer.

HEART

ATHEROSCLEROSIS AND CORONARY HEART DISEASE

Although there is abundant evidence that elevated blood levels of cholesterol and other lipids increase susceptibility to atherosclerosis and coronary heart disease, it remains to be established whether reducing blood lipids by dietary modifications or other means can halt or reverse the disease process and thereby reduce heart-disease risk.

NHI grantees studied this problem by feeding rabbits an atherosclerosis-producing (atherogenic) diet containing radioactive cholesterol for 14 weeks. At this time the control animals were sacrificed, their blood and tissue analyzed for cholesterol, and their aortas graded for atherosclerosis. The other animals were then placed on lipid-lowering diets low in fat or high in polyunsaturated fats (corn oil) for an additional 40 weeks.

In most animals, both diets reduced serum cholesterol levels to normal and held them there for 6 months. However, when the animals were sacrificed at 40 weeks, the scientists observed no net movement of labeled cholesterol out of the aortic wall and no amelioration of the atherosclerotic lesions, even though the cholesterol content of other organs had declined greatly during this period.

Cholestyramine is a non-absorbable resin that forms insoluble complexes with bile acids in the intestine and facilitates their elimination in the feces. Bile acids are the major pathway for cholesterol excretion, but a high proportion of bile acids produced through the oxidation of cholesterol are reabsorbed. Further bile acids also appear to play an important role in the absorption of dietary fats.

By increasing the fecal excretion of bile acids, cholestyramine causes additional cholesterol to be diverted into bile-acid production at the expense of blood cholesterol and may hinder absorption of fats that tend to increase plasma cholesterol levels.

Cholestyramine was tested in dogs fed an atherogenic diet that produced cholesterol levels of 742–836 mg/100 ml. of plasma in untreated control animals. When the treated group was given 12 grams of cholestyramine per day, their plasma cholesterols fell to 493; increasing the dosage to 24 grams daily reduced them to 257 over the next 8 months.

All control animals died within 6–9 months, and 6 of 9 had marked atherosclerosis. Three cholestyramine dogs sacrificed after 9 months were free of atherosclerosis.

The two studies, taken together, indicate that established atherosclerosis is likely to respond slowly, if at all, to measures that reduce plasma levels of cholesterol and other lipids, although such measures may halt or retard further progress of the disease. However, if plasma-lipid levels are prevented from becoming elevated in the first place or elevated blood lipids corrected early, the chances of preventing atherosclerosis are greatly enhanced.

The "combination of ingredients" approach to therapy, previously used with considerable success in the clinical management of hypertension, may also be applicable to the control of elevated blood levels of cholesterol, NHI grantee studies suggest.

Using the lipid-lowering drugs CPIB and D-thyroxine separately, then in combination in 12 subjects with hyperlipemia and coronary heart disease, the scientists found the combination to be more effective than either drug alone in reducing blood cholesterol levels. CPIB alone reduced these levels by about 12%, D-thyroxine by about 14%, but the combination achieved a reduction of about 20%. CPIB alone also reduced blood triglycerides, but this effect was not enhanced by the addition of D-thyroxine.

Although the effects of the combination on blood lipids were not remarkable, the results do suggest that dietary modification plus combinations of compatible drugs that lower plasma lipids by different mechanisms may improve medical control over hyperlipemia that does not respond well to individual therapeutic measures.

A study originally designed to assess the relationship between dietary habits and heart-disease risk has disclosed that occupational stress may also be a potent factor affecting the development of coronary heart disease and such dangerous complications as heart attacks.

The study compared a large group of Benedictine Monks, who eat a typical American diet, with a similar group of Trappists, who eat a frugal lacto-vegetarian diet considerably lower in fat. Not unexpectedly, the Trappists as a group had substantially lower plasma lipid levels than did the Benedictines and experienced only about one-third as many episodes of coronary heart disease.

However, the study also disclosed that as monks from either group moved up to higher echelons within their order, their heart-disease risk increased steeply even though their dietary habits remained essentially the same. For example: the age-standardized rate of coronary heart disease prevalence among Trappist fathers (29.4 per 1000) was more than than three times that among Trappist brothers (8.5 per 1000). Similarly, among Benedictine fathers, the age-standardized prevalence rate was 85.7/1000 if they remained in the monastary, 99.5/1000 if they resided outside; whereas among Benedictine brothers it was only 34/1000.

Cigarette smoking is strongly associated with increased mortality from coronary heart disease, but how the smoking habit exerts its harmful effects has not been established. Data from the Framingham Study have suggested that smoking does not appreciably influence the development of coronary atherosclerosis, but may be a trigger factor in such calamitous complications as heart attacks or potentially lethal abnormalities of heart beat.

However, in a recent study correlating autopsy findings with smoking habits during life in 645 males, aged 20–64, who had died from causes other than complications of cardiovascular disease or from diseases strongly associated with smoking (lung cancer, emphysema, etc.), NHO grantees found evidence that smoking may, in fact, accelerate the development of coronary heart disease. In extent and severity, coronary atherosclerosis was greatest among heavy smokers (25 or more cigarettes a day), intermediate among lighter smokers (less than 25 cigarettes a day), and least among non-smokers. Differences between the groups tended to be most pronounced in the younger age brackets.

Other NHI grantee studies suggest a possible mechanism by which smoking may precipitate certain of the often-deadly complications of established coronary heart disease. The scientists observed that mixed-thrombus production (the white portion consisting mainly of aggregated blood platelets, the red portion of fibrin and other blood components) occurred far more rapidly in blood samples obtained from smokers than from non smokers. They reasoned that, since smoking is a potent stimulus for catechol-amine release from tissue stores, these amines (norepinephrine and epinephrine) might accelerate mixed-thrombus development by promoting platelet aggregation.

Addition of the same compounds *in vivo* did, in fact, markedly accelerate thrombosis in animals. When the agents were added to blood samples *in vitro*, thrombosis was moderately accelerated in only a few instances; but, when added to plasma from the same blood samples, these amines produced rapid phatelet aggregation.

Platelet thrombi are usually transient, but may provide a nidus for the formation of longer-lived clots. Further, earlier grantee work has indicated that even short-lived platelet thrombi induced in the coronary blood vessels of animals can trigger severe symptoms of blood deprivation, dangerous arrhythmias, and even death.

This study does not purport to link platelet aggregation observed in the test tube to coronary occlusion in man, but it raises some possibilities that might be profitably explored in further studies.

NHI grantees report that subjects who have experienced heart attacks or clinical symptoms of angina pectoris may also exhibit a subtle abnormality of the hemoglobin of their red blood cells. Although its uptake of oxygen under physiological conditions is not impaired, it is distinctly more reluctant than is normal hemoglobin to surrender its oxygen under conditions of acidity approximating those prevailing in the capillaries.

This abnormality was observed in blood from all 11 patients with heart disease, whether or not they smoked; but it was also observed in 2 smokers without heart disease, and the abnormality was more pronounced in the heavier smoker. It was observed in none of the 12 healthy controls, 2 of whom were light smokers.

These observations raise the possibility that subjects with reduced coronary bloodflow due to atherosclerosis may be laboring under still another handicap: the hemoglobin abnormality may render the heart less capable of extracting oxygen from the blood that does get through. Whether this phenomenon is a general characteristic of artherosclerotic heart disease, contributes to its symtomology, or is worsened by smoking is unknown, but it certainly deserves further study, the scientists conclude.

The presence of angina pectoris in women of childbearing age does not necessarily denote precocious atherosclerosis of the major coronary arteries, NHI grantees report. They cite their findings in 14 women, 34–43 years old, all of whom were considered on clinical grounds to have unmistakable coronary heart disease. All had expereienced angina requiring nitroglycerine for 1–3 years. Marked electrocardiographic abnormalities suggestive of coronary heart disease were observed at rest and were exaggerated by graded exercise.

However, when substances opaque to x-rays were introduced into the coronary arteries and followed by rapid-sequence x-rays, the resulting angiograms disclosed no evidence of atherosclerosis or any other abnormalities in any of the major branches of the coronary tree.

The causes of the angina and electrocardiographic abnormalities could not be determined, but may involve congenital abnormalities, spasm, or blockade of blood vessels at the level of the finer coronary branches or microcirculation. If so, the condition indeed differs markedly from ordinary coronary atherosclerosis, which tends to attack the proximal portions of major vessels and to leave the deeper branches relatively unscathed.

The scientists feel that many cases of apparent coronary atherosclerosis in younger women may fall into this category. Its mode of treatment and clinical outlook are unresolved, but may differ in both particulars from atherosclerosis of the major coronary arteries.

In hypertrophic subaortic stenosis (HSAS), the muscular walls of the left ventricle are considerably thickened in the region of the outflow tract just below the aortic valve. During the left ventricle's pumping stroke, the contraction of this mass of muscle exerts a constrictive action that hinders the ejection of blood through the aortic valve. The more vigorous the pumping stroke, the severer the degree of obstruction.

Exercise, which increases the oxygen needs of the heart, also aggravates outflow constriction and compromises coronary bloodflow in HSAS patients, frequently bringing on severe angina pectoris. NHI scientists report that the exercise tolerance of HSAS patients can often be substantially increased by propranolol. This drug selectively blocks those nerve receptors which mediate the increases in heart rate and the vigor of heart-muscle contraction normally resulting from exercise.

Five of 6 patients were substantially benefited by the drug in the performance of treadmill exercise. These patients walked for an average of 10.5 minutes and managed a 10% upgrade before onset of angina on days that they received propranolol. On placebo days, they lasted only 6 minutes and managed only a 5% upgrade.

Abnormalities in heart rhythm, which may arise unexpectedly and progress swiftly through chaotic, ineffectual contractions (fibrillation) to cardiac arrest, are a common death-dealing mechanism among hospitalized heart-attack patients. Quinidine and other anti-arrhythmic drugs are often used to control such arrhythmias after they have developed, but little information has been accumulated concerning the potential value of such drugs in preventing arrhythmias in heart-attack victims.

NHI grantees examined the prophylactic value of quinidine in pigs subjected to gradual occlusion of a coronary artery by an Ameroid constrictor that, when placed around a blood vessel, gradually swells to block the vessel after 24–48 hours. Seventeen pigs received quinidine in saline every 6 hours, the 11 controls received only saline. The grantees state that the prophylactic use of quinidine increased survival (5 of 17 treated versus 2 of 11 controls) and, among animals who died, increased the mean survival time from 15 to 32 hours.

Fibrinolytic drugs, which bring about the dissolution of blood clots either by attacking them directly or by activating the body's own clot-lysing mechanisms, may hold great promise in the clinical management of such clotting complications of cardiovascular disease as heart attacks, certain strokes, pulmonary embolism, and peripheral blood-vessel thrombosis. The most promising fibrinolytic agent developed thus far is urokinase. This substance, derived from human urine, works by activating the body's clot-lysing mechanisms. It is currently slated for extensive clinical trials against a number of thromboembolic disorders in a large NHI-supported collaborative study.

Earlier experimental evidence has suggested that fibrinolytic therapy was likely to be ineffective unless initiated early. It appeared that, within 72 hours, clots or emboli became extremely resistant to the attack of such agents. However, recent studies by NHI grantees suggest that at least some clots remain susceptible to lysis even when 7–14 days old.

In these studies clots were induced in the inferior vena cava of dogs. After 5–14 days of "aging" in the blood vessel, they were removed, weighed, measured, and photographed, then introduced into the pulmonary circulation of other dogs. Some of these animals were untreated, the rest infused for 8–12 hours with urokinase sufficient to produce intense fibrinolytic activity in the blood.

The fibrinolytic mechanisms of untreated animals were able to achieve 15–20% dissolution of 7-day-old clots in 24–48 hours, and 10–25% dissolution of 14-day-old clots over the same periods. But the urokinase-treated animals achieved 80–100% dissolution of 7-day-old clots and 50–80% dissolution of clots two weeks old.

Gas endarterectomy, a technique previously used successfully to open up peripheral blood vessels partially or wholly obstructed by atherosclerosis, may improve the safety and effectiveness of surgery to improve the blood supply to the heart muscle by a direct attack on diseased coronary arteries, NHI grantees report.

In this technique, a needle is passed through the healthy outer layer (adventitia) of the artery. Carbon dioxide is then forced through the needle, creating a gas pocket that divides the adventitia from the diseased inner layers (media and intima) of the vessel. As more carbon dioxide is forced in, the pocket spreads along this cleavage line, cleanly separating the healthy and diseased layers. Any gas escaping into the blood would be quickly dissolved.

Long segments of diseased vessels can be swiftly and safely stripped of diseased cores, which are withdrawn and cut free through small incisions. Although the technique strips the arterial segment of most of its muscle, the grantees report that ballooning or rupture of treated vessels has not occurred to date.

Recently, the technique has been tested successfully in more than 50 diseased cadaver hearts. Diseased cores up to 5 inches long, many with side branches, have been removed from the coronary arteries through short proximal incisions.

Angiograms and careful dissection studies suggest that the gas endarterectomy technique may eliminate some of the difficulties and hazards of conventional surgical stripping techniques.

HYPERTENSION

Cadmium, a trace metal with no known biological function, may play an important, though undefined role in the development of essential hypertension, an NHI grantee reports. Cadmium is found in minute quantities in air and in many foods and beverages. When ingested, it tends to accumulate in the kidneys. Previously, autopsy studies indicated that the kidneys of patients dying from hypertension and its complications usually contained higher cadmium concentrations than those of subjects with normal blood pressure.

Subsequent studies have shown that rats, given trace quantities of cadmium in their drinking water, develop hypertension strikingly similar to essential hypertension in humans. The disease usually appears after about one year of life (roughly equivalent to age 30 in humans), the incidence increasing with age. Female rats are more susceptible than males, but the males seem to be hit harder by the disease and have higher mortality rates. Hypertensive rats exhibit renal cadmium concentrations in the same range as those found in Americans.

The development of cadmium-induced hypertension was inhibited by the concurrent addition of calcium to the animals' drinking water and could be reversed by metal-binding agents that facilitated the excretion of renal cadmium.

Whether these findings will prove applicable to human hypertension is not known; but they point up a potential cause and also a potential means of therapy for one of mankind's most prevalent disorders.

Patients whose hypertension becomes unresponsive to maintenance doses of antihypertensive drugs may be managed successfully by hospitalization at intervals for 20-day programs of intensive drug therapy, NHI grantee studies indicate.

The 16 patients in this series had severe hypertension (mean arterial pressure: 178 mm/Hg) that persisted despite oral hypotensive medication that had been steadily increased until the dosages reached toxic levels. Most had developed retinal hemorrhages, heart enlargement, or overt congestive failure.

Upon hospitalization, the patients were treated for 20 days with large intravenous injections of diazoxide (a thiazide drug with potent blood-pressure effects but little diuretic action), which were given as often as necessary to reduce blood pressure by 25% or more and to hold it there throughout the hospital stay. Upon discharge, the patients were maintained on reserpine plus diuretic therapy, returning to the hospital from time to time for repeated courses of intensive diazoxide therapy.

After 30 months, the scientists report, mean arterial pressures in these patients had been reduced by more than 50 points, retinal hemorrhages and congestive failure had cleared completely, and heart enlargement had been reduced in all patients.

In patients with malignant hypertension and kidney failure, it is essential that blood pressure be reduced to halt or retard progressive blood-vessel damage, event though lowering of the patient's blood pressure may further impair the function of his damaged kidneys. NHI grantees report that the use of chronic peritoneal disalysis in conjunction with hypotensive therapy may be life saving in some of these cases.

Seven patients so treated showed immediate clinical improvement. Moreover, the salt and water removal by dialysis also facilitated blood-pressure control. In three patients, there was some evidence of improvement of blood-vessel lesions and marked improvement in kidney function. Of these, one survived for at least a year after discontinuing dialysis, then was lost to followup; a second has done well without dialysis for at least 2 months; and a third, though improved, still requires dialysis.

This series, though small, suggests the value of dialysis as a life-support technique that makes possible heroic measures for blood pressure control in malignant hypertension complicated by kidney failure.

A dissecting aneurysm occurs when damage or a weakness in the inner layers of the blood vessel wall enables blood to force its way between the layers. Thus blood pressure in the vessel is exerted, not on a single strong muscular wall, but on separate thin layers that may not be able to withstand it. The danger of rupture and fatal bleeding is especially grave in dissecting aneurysm

of the aorta. Unfortunately, surgery to correct such aneurysms is also risky, with mortality rates ranging from 25–40%.

NHI grantee studies indicate that some cases of dissenting aneurysm of the aorta may be managed non-surgically with blood-pressure-lowering drugs. The 9 patients in this study were 44–88 years old and had systolic blood pressures ranging from 165–240 mm/Hg. Using a combination of hypotensive agents, the scientists drove these pressures down to 110–130 mm/Hg and held them at these levels during the period of hospitalization. Since discharge, the patients have been maintained on chlorothiazide and guanethidine, a combination that has kept their blood pressures under 135 mm/Hg.

During monthly checkups, chest x-rays have revealed no progressive enlargement of the aorta, and no symptoms of aortic insufficiency or other indications for surgical intervention have developed during followup periods of 4–11 months. Although the series is small, the early results have been encouraging enough to suggest that, in selected cases, conservative management with hypotensive agents may offer an alternative to surgery for dissecting aneurysm of the aorta.

Hypertension, hypertensive heart disease, and other evidence of heart disfunction greatly increase the indiivdual's risk of stroke, data from the Framingham Study indicate.

Hypertension was the factor most strongly associated with stroke, being present in 60% of patients suffering strokes during the 12-year period of study. But patients who had previously experienced heart attacks, who had congestive heart failure, or who were diabetic also developed a marked excess of strokes. And certain EKG abnormalities previously found to be associated with increased heart-disease risk appeared to herald even greater risk of stroke, whether or not hypertension was also present.

The observation that 50% of the stroke victims either had or soon developed other manifestations of atherosclerosis indicates that cerebrovascular disease is, after all, part of the larger problem of cardiovascular disease. In most particulars, the subject who is coronary prone is likely also to be stroke prone, and therapeutic measures aimed at reducing the risk of one are as likely to reduce the risk of the other.

CONGESTIVE HEART FAILURE

The heart enlargement that usually precedes and accompanies the development of congestive heart failure increases total heart muscle mass, but there has been some dispute over whether these muscle fibers are functionally normal or whether increases in quantity are accompanied and partially offset by decreases in quality.

NHI scientists report that heart enlargement depresses contractility per unit of heart muscle. This depression was most profound in muscle from failing hearts, which contracted less rapidly and developed significantly less tension than did muscle from normal hearts. In enlarged, but nonfailing hearts, the scientists found, the increase in total heart-muscle mass may compensate for the reduced contractility of individual elements—for a time. But, as enlargement continues, mechanical factors come into play that inexorably reduce over-all pumping efficiency of the heart, whatever its total muscle mass or the contractile state per unit of muscle. This, coupled with aggravation of the basic contractility defect, forces the heart into failure.

Prolonged, excessive alcohol consumption is an important cause of primary myocardial disease (PMD), a degenerative process predominantly affecting the heart muscle and often leading to congestive heart failure. In a series recently reported by an NHI grantee, 83 of 100 individuals with PMD in the Minneapolis Veterans Hospital were chronic alcoholics, predominantly heavy beer drinkers.

Heart tissue samples were obtained by needle biopsy from 50 of these patients for comparison with tissue specimens from 20 patients undergoing surgery for rheumatic valvular disease and from 2 non-alcoholic patients with PMD.

Electron microscopy of samples from alcoholic patients revealed striking cellular and intracellular alterations not observed in the other tissue specimens. Some heart-muscle fibers were completely obliterated, others fragmented into short contracted segments. Mitochondria, the intracellular structures that generate most of the chemical energy that powers heart-muscle contraction, were swollen, often enlarged to twice or three times normal size, and structurally damaged, giving them a moth-eaten appearance. These observations suggest that, in alcoholic myocardial diseases, heart failure may stem both from the loss of

functioning heart muscle mass and from impairment of energy-yielding processes needed for normal contraction.

NHI grantees report experimental results with a new approach to the management of right-heart failure that may prove applicable to clinical problems posed by irreversible pulmonary hypertension due to inoperable congenital heart defects or to chronic lung diseases such as emphysema.

Earlier results had shown that venous hypertension, edema, and ascites (fluid accumulation in the abdominal cavity) could be dramatically, though temporarily, relieved by removal of lymph through a catheter placed in the thoracic duct. This duct, located at the junction of the subclavian and jugular veins, is a major portal of entry for lymph returning to the circulation.

Since the high systemic venous pressure resulting from right-heart failure hinders the re-entry of lymph by its normal route, the grantees reasoned that a major cause of fluid accumulation might be eliminated by redirecting thoracic duct lymph into a lower-pressure vein. Accordingly, they spliced the thoracic duct into the left superior pulmonary vein in 8 dogs with surgically induced right heart failure. The low pressure in this vessel facilitated the entry of lymph via the shunt, greatly increasing kidney excretion of salt and water and rapidly reducing venous hypertension and ascites. In one animal, the shunt became blocked and the manifestations of right-heart failure reappeared, but as long as the shunts remain open they appear able to keep such manifestations under control.

Norepinephrine increases heart rate and the vigor of heart-muscle contraction but also causes blood-vessel constriction that reduces the overall effect of norepinephrine on heart output and coronary bloodflow while increasing the cardiac workload. NHI grantees report that using norepinephrine to augment cardiac output plus phentolamine to counter its vasoconstrictive action increased coronary bloodflow by as much as five times without significantly increasing the workload on the heart in animals with shock resulting from induced heart attacks.

Dopamine, the chemical precursor of norepinephrine, is a potent cardiac stimulant 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.

HEMORRHAGIC DISEASES

The coagulation defects of classical hemophilia and other hereditary bleeding disorders resulting from clotting-factor deficiencies can be corrected (temporarily) only by supplying the missing factor through transfusion of whole blood, plasma, or clotting factor concentrates.

The clotting factors most urgently needed are antihemophilic globulin (AHG), deficient in classical hemophilia, and plasma thromboplastin component (PTC), deficient in Christmas disease. Together, these diseases account for about 90% of all hereditary bleeding disorders.

AHG is such an unstable protein that only the freshest blood or plasma has been relied on as a source of this factor. PTC is more stable, and ordinary banked blood or plasma has been considered a suitable source. However, recent studies by NHI grantees have disclosed that the plasma from outdated bank blood is a largely untapped source of AHG, PTC, and a number of other clotting factors of clinical importance.

In these studies, the AHG levels of such plasma samples averaged 56% of normal, and, in about one-third of the samples, exceeded 70%. The PTC levels of these plasma samples consistently exceeded 70%, as did levels of several other clotting factors.

Plasma from outdated bank blood has been used as a source of some protein fractions, but not for the therapy of hemorrhagic diseases. These findings suggest that such plasma is a suitable source for several clotting-factor concentrates. Moreover, it may be transfused without screening for clotting-factor levels in the treatment of Christmas disease and hemorrhage due to deficiencies of prothrombin or factors VII and XI. Such plasma is also often suitable for transfusion in hemophiliacs, although such use should be preceded by tests of AHG activity.

An extremely sensitive and relatively inexpensive device originally developed to detect freon leaks in refrigeration equipment also provides a simple, safe, and rapid means of detecting left-to-right cardiac shunts. Such shunts, usually the result of congenital defects in the muscular wall (septum) that divides the heart into two pumping systems, are one of the most commonly encountered signs of congenital heart disease.

A cardiac catheter is passed into the right side of the heart. The patient then takes a single breath of freon and the catheter is connected to the detector, which samples a small amount of blood from the right heart. The presence of freon in the sample means that some of the blood returning to the left heart from the lungs has passed into the right heart through a septal defect. The freon detector is so sensitive that even very small shunts are immediately revealed by the technique. Moveover, freon gas is non-toxic and non-explosive and is removed so rapidly from the blood that multiple determinations can be made with no loss of diagnostic sensitivity.

A fiber optic catheter system, developed by the American Optical Company, has been used clinically by NHI scientists to obtain instantaneous and continuous measurements of the oxygen content of blood within the heart, great veins, and pulmonary arteries. It has proved to be a simple, highly accurate means for detecting and evaluating the magnitude of left-to-right shunts and for assessing the effects of exercise, drugs, and other interventions on such shunts. It has also been highly useful for studying oxygen saturation and blood pressures in the pulmonary arteries of exercising patients with varying degrees of heart impairment.

The catheter contains two fiber optic bundles, which can channel light much as a wire channels electricity. Light is piped directly into the right heart chambers through one bundle. Some of it bounces off red blood cells in the heart and is reflected back through the other fiber optic bundle to the recording equipment. Each bundle is equipped with a special filter that allows light of only one selected wavelength to pass. On one wavelength, the amount of light reflected by red blood cells varies with the oxygen saturation of the hemoglobin they contain. The other wavelength is not so affected. The oxygen content of the blood is determined by comparing the intensity of the two beams, an operation performed automatically by the system about 10 times per second.

With appropriate changes in filters, the system can also record dye dilution curves within the heart. The dye (indocyanine green) is injected into a peripheral vein. As it passes through the right heart on its way to the lungs, its concentration is continuously recorded. Normally, the dye concentration will plot as a curve with a sharp upslope, then, as the dye is cleared from the right heart, a smooth, gentle downslope. If a left-to-right shunt exists, some of the dye returning to the left heart from the lungs will cross over into the right heart, causing a second peak in the dilution curve. Unlike conventional dye dilution techniques, this method does not require withdrawal of blood samples.

Like the conventional catheter, the fiber optic catheter has a lumen through which blood pressures can be continuously recorded, contrast substances or other agents injected, or blood samples withdrawn. The system thus has great versatility in research or clinical use.

Large left-to-right shunts due to ventricular septal defects overload the pulmonary circulation, resulting in pulmonary hypertension that can cause damage to the blood vessels of the lungs and a heavy strain on the right ventricle. Pulmonary hypertension also substantially increases the risk of surgery to correct such septal defects. NHI grantees report that the effects of such shunts on the pulmonary circulation are determined, not only by the magnitude of the shunt, but also by the direction taken by the stream of blood as it enters the right ventricle.

In 16 children with isolated ventricular septal defects, substances opaque to x-ray were introduced via catheter into the left heart, then followed by motion pictures to determine bloodflow patterns through these defects. When correlated with other data, the cineangiograms showed that, if the stream of blood was directed toward the right ventricular outflow tract and pulmonic valve, the shunt resulted in more rapid ejection of blood by the ventricle and raised systolic pressure in the pulmonary artery (normally only 30-35 mm. of mercury) to levels approaching systemic pressure (about 120 mm/Hg.). If the stream was oriented primarily toward the right ventricular inflow tract and tricuspid valve, however,

the effects of the shunt on right-ventricular contraction and on the pulmonary circulation were relatively slight. Shunts oriented toward both inflow *and* outflow tracts had intermediate effects on right ventricular contraction and pulmonary pressure.

The results suggest that determinations of patterns of flow as well as volume of flow through ventricular septal defects can provide information of considerable value in determining whether, or when, to undertake surgical correction of such defects.

RHEMUATIC HEART DISEASE

Although surgery for the correction of aortic-valve regurgitation due to rheumatic fever has become ever safer and more effective during recent years, such surgery does carry definite risk that may not be justifiable in some cases, NHI grantees report.

This conclusion is based on a study of 323 patients with pure aortic regurgitation who did not undergo surgery. The long-term prospects of these patients were evaluated to develop prognostic criteria of value in identifying those patients in whom surgery is indicated or mandatory and those in whom it may be safely postponed or foregone.

The clinical features found to be of greatest value in making such judgments were heart size, diastolic blood pressure, the characteristics of the T wave of the electrocardiogram, heart failure, or angina without failure.

For patients with greatly enlarged hearts, diastolic pressures below 40 mm/Hg. inverted T waves, congestive failure, or angina, the outlook was grave. Mortality was 31% over 5 years and exceeded 50% over 10 years. In patients with heart failure, 13 of 14 succumbed within 2 years. Hence, in patients with symptoms such as these, the risk of surgery is far outweighted by the risk of foregoing it.

However, among patients with only slight to moderate heart enlargement, normal to moderately low diastolic pressure, and normal T waves, 20-year survival was 100%. Among patients otherwise similar but with low diastolic pressure, 5-year mortality was 11%, 10-year mortality 27%. In the first group, the scientists conclude, surgery is not indicated at all; in the second group, it is justified when the expected 5-year mortality among patients undergoing surgery falls to 10% or better.

Although a variety of clinically reliable artificial valves have been developed during recent years, and though artificial valves are used in the overwhelming majority of valve-replacement situations, some surgeons have maintained that healthy valve homografts are clinically superior to any artificial model yet devised.

NHI grantees recently reported their results with aortic-valve homografts inserted in 41 patients. There were three hospitals deaths and 1 late death in this series, none attributable to malfunction of the valve. All 38 survivors have had excellent clincial and hemodynamic results. The only residual abnormality has been a sort diastolic murmur in 10 patients. No anticoagulants have been used and no evidence of clotting complications has developed. The grantees state that insertion of the valve homograft is more difficult than insertion of an artificial valve, but the superior clincial results make it the operation of choice for aortic-valve disease.

The mitral valve, lying between the left atrium and left ventricle, has been thought to be composed only of fibrous and connective tissue and its opening and closing a purely passive response to blood-pressure changes within the two left-heart chambers. However, NHI studies have shown that the mitral leaflets are endowed with muscle fibers and with nerves, and the leaflet musculature responds to mechanical, electrical, and chemical stimuli in a manner analogous to heart-muscle fibers.

Mitral valve leaflets actively contracted during electrical stimulation, and the vigor of these contractions could be augmented by norepinephrine, digitalis, and other drugs or procedures that augment heart-muscle contraction. Similarly, mitral muscle fibers contracted more vigorously from longer initial fiber lengths than from shorter ones, indicating mechanical properties like those of heart muscle. That the nerve supply to these leaflets was functional was suggested by the presence of releasible catechol amines, which function as the chemical mediator of sympathetic nerve impulses.

Whether or to what extent the active contraction of the mitral valve affects either mitral-valve performance or left-heart function in health or disease remains to be determined; but these unexpected observations suggest that some reassessment of mitral-valve function may be called for.

A significant number of patients with severe mitral valve disease also have evidence of tricuspid regurgitation (28 of 100 in a recent NHI series). Thus whether to replace the malfunctioning tricuspid valve at the time of mitral-valve surgery is a problem often confronting the surgeon.

Unless the regurgitation is due to immobilization of the valve leaflets by scar tissue secondary to rheumatic inflammation, repair or replacement of the tricuspid valve is seldom necessary, NHI surgeons report. Otherwise, the regurgitation usually stems from dilation of the valvular orifice due to elevated blood pressures in the pulmonary circulation and right ventricle. These conditions are usually corrected by mitral valve replacement, after which the tricuspid malfunction will improve or disappear with time.

Of the 28 patients whose tricuspid regurgitation was not corrected in conjunction with mitral valve replacement, 24 have survived. This operative mortality was no higher than that among patients without tricuspid regurgitation. Of 23 survivors followed from 4–48 months, all have shown clinical improvement and 17 have experienced reduction in right atrial pressure indicative of improved tricuspid function. In 13, right atrial pressures have returned to normal.

Clots forming on artificial heart valves are an important cause of disability and death in patients surviving the immediate postoperative period. The risk of clotting complications is especially high after mitral or tricuspid replacement, and the patient may have to be kept on anticoagulants indefinitely. More streamlined valve designs and the use of non-wettable materials have not solved this problem.

NHI scientists reasoned that better results might be achieved by encouraging the ingrowth of host tissue on all fixed parts of artificial valves, thereby creating a "native" surface more compatible with blood. Accordingly, they covered the bases, cages, and struts of ball or lens valves with loose-weave polypropylene or Dacron fabric. These modified valves were used to replace tricuspid, pulmonic, or mitral valves in 21 calves. Unmodified valves were inserted in these positions in 12 control animals. None of the animals received anticoagulants postoperatively.

There has been no evidence of postoperative clotting complications in the animals receiving modified valves. Six animals were sacrificed 7 weeks to 3 months postoperatively. The fixed valve parts had become coated with thin layers of glistening, transparent tissue that were completely free of clots. This tissue in no way interfered with the action of the moving parts. In contrast, 3 control animals succumbed to clotting complications within 4 months, and in 7 others clots of various sizes were found on valve cages at the time of death or sacrifice from 1 day to 2 years postoperatively.

Low molecular weight dextran (LMDx) is a plasma expander that has also been used clinically in lieu of blood for priming heart-lung machines and to reduce the threat of clotting complications after heart-valve replacement. However, NHI grantees noted that the therapeutic use of LMDx in three patients with reduced kidney bloodflow but adequate urinary output was followed shortly by acute renal shutdown. Since LMDx increases the viscosity and specific gravity of urine, the scientists reasoned that, under conditions of reduced renal bloodflow, LMDx might produce blockade of the kidney tubules and halt the elaboration or urine.

This hypothesis was tested in dogs in whom one renal artery was constricted by 50%, the other was not. Subsequent intravenous infusions of LMDx caused 6 of 8 blood-deprived kidneys to stop excreting urine altogether (anuria) and the two others excreted markedly diminished amounts for at least two hours. Releasing the arterial constriction in 2 anuric animals did not result in urine production.

Postmortem examination of the blood-deprived kidneys revealed some syrupy urine in the renal pelvis and LMDx precipitates clogging the kidney tubules. The control kidneys exhibited none of these abnormalities. The grantees conclude that LMDx therapy is hazardous in patients with reduced renal bloodflow because it may precipitate acute renal failure.

ARTIFICIAL ORGANS

The lack of materials compatible with blood has hampered progress in the design and development of artificial heart and heart assist devices, artificial heart valves, and other spare parts for the cardiovascular system. All materials tested to date have tended to damage cellular elements of blood, denature blood proteins, and promote clot formation.

Recent research has demonstrated that certain materials can be made more thrombus resistant by treating them with graphite, benzalkonium, and heparin. Plastic surfaces receiving this treatment present to the blood an extremely thin layer of heparin, probably only one molecule in thickness. This naturally occuring anticoagulant appears to protect against thrombus formation—at least while it lasts.

Recent NHI studies indicate that it doesn't last long. Plastic beads treated in this fashion (using radioactive heparin for tracer purposes) were incubated in saline or plasma with constant agitation or were implanted into the left atria of dogs. The implanted beads lost 71% of their labeled heparin within 4 hours and retained less than 5% after 36 days. The heparin loss was somewhat slower in the *in vitro* experiments, but not much; after four days of incubation, only 10% remained. These findings indicate that monomolecular layers of heparin on plastic surfaces are likely to provide only very brief protection against clotting.

Determination of the breakdown of blood cells detectable immediately after pumping whole blood by one or another mechanical device affords but meager measure of the extent of blood damage actually produced by such devices, NHI-supported scientists report.

For every blood cell actually destroyed by such devices, another four have sustained damage that, while not immediately lethal, will substantially shorten their survival. Such damage is manifested by sharp increases in cellular metabolic rate, release of free fatty acids, increased fragility, and delayed hemolysis. In these studies, even pumps considered to have gentle blood-handling characteristics produced rates of delayed hemolysis that probably exceeded the regenerative capabilities of the animal. This extensive blood-cell damage constitutes one of the principal deterrents to prolonged use of mechanical blood pumps of current design, or constructed of currently available materials.

NHI-supported animal experiments indicate the body is capable of dissipating the heat generated by an implantable power source for driving an artificial heart, even when heat tolerance is further taxed by fever or vigorous exercise.

It has been calculated that the power source for an artificial heart must deliver 1.5–4 watts of continuous power for routine heart operation and up to 7 watts to meet the increased demands imposed on the pump by vigorous exercise. Since even the best power sources are likely to have energy conversion efficiencies no higher than 15%, some 10–25 watts wil be continuously wasted as heat, which the body must absorb and dispose of. Most systems proposed thus far plan to use the blood to absorb this heat, leaving to thermoregulatory mechanisms of the body such details as eliminating as much as possible and adjusting to the rest.

This may not be taking too much for granted, the animal experiments showed. When electrical heating tubes that generated 4–24 watts of power were placed in the aortas of healthy dogs, even maximum power for prolonged periods failed to raise body temperature by more than 1°C. The function of various organs (heart, liver, kidney) were not adversely effected. Blood cells and blood chemistry did not appear to be appreciably affected unlesss the temperature at the blood-heat exchanger boundary exceeded 42.6°C, when clots formed on the exchanger in two instances. When boundary-layer temperatures were held below this level, clotting complications did not occur.

Animals have survived this heat duress for more than 6 months without any evidence of adverse effects on physiological function. Even when additional heat stresses were imposed (induced fever, vigorous treadmill exercise), the animals' thermoregulatory mechanisms proved equal to the challenge.

NHI-aided scientists report that their electro-hydraulic total heart replacement has reached the stage of long-term testing in animals. Its size has been reduced enough to allow implantation of the blood pump within the chest cavity and the weight of the pump (when filled) reduced to less than 3 pounds. The pump is powered by an external electric motor that energizes the heart via wires passing through the chest wall. The electric motor, batteries, and other components are small enough to fit into a briefcase.

The electric motor energizes a hydraulic system that alternately compresses first the pulmonary then the systemic pumping chamber by forcing hydraulic fluid into the rigid housing surrounding the collapsible ventricles. The transfer of fluid from one side of the heart to the other enables the ventricles to refill between pumping strokes. Controlling the hydraulic system is a magnetic fluid valve that continuously monitors and responds to venous return, adjusting the

flow of hydraulic fluid as necessary to increase or decrease pump output and to balance pulmonary and systemic bloodflows.

The pump can deliver up to 12 liters of blood per minute. Through duplication of essential systems, the pump can maintain an output of 5 liters per minute even though one of the primary systems should fail. Animals have been maintained by this pump for as long as 18 hours.

NHI scientists have developed a miniature oxygenator for use in conjunction with isolated organ perfusion or regional perfusion in cancer chemotherapy. Such perfusion techniques make it possible to deliver antitumor agents in high concentrations to tissues affected by cancer while sparing healthy organs and tissues from the cellular toxicity of such agents. The oxygenator assures an ample supply of oxygen to the tissues under perfusion while they are cut off from their normal blood supply.

The oxygenator contains a thin envelope of silicone rubber mounted on a screen of Dacron mesh. This envelope has excellent gas-exchange characteristics and is also inert to blood. As blood flows over the outer surfaces of the envelope, oxygen is continuously sucked through the envelope by the application of low negative pressure. Oxygen diffuses through the envelope to the blood flowing down its surface while carbon dioxide from the blood diffuses into the envelope and is swept out by the continuous oxygen stream.

The device is currently undergoing experimental evaluation by NHI and NCI scientists.

NHI scientists are also experimenting with a suction-operated device for providing temporary or permanent pumping assistance to hearts incapacitated by damage, disease, or severe arrhythmias. The device is designed to fit snugly around the two main pumping chambers of the heart. It consists of a rigid outer housing whose dimension are approximately those of the left and right ventricles when relaxed and filled. The inner housing is elastic, and its dimensions approximately those of the ventricles when fully contracted.

When strong suction is applied on the rigid outer housing, the elastic inner housing is stretched outwards until its configuration is the same as that of the outer housing. When the suction is released, the inner housing snaps back to its original configuration. Hence, applying suction during the heart's filling phase gives the ventricle room to expand and fill; releasing it during the contraction phase uses the elastic recoil of the inner housing to assist the ventricles in expelling blood.

The device has been tested in dogs with normally beating hearts and also with induced ventriclular fibrillation. It has maintained normal heart output and blood pressure during fibrillation for periods up to 11 hours after which defibrillation was successful.

Fixed rate pacemakers may deliver pacing impulses to the heart by means of electrodes implanted in the heart through an incision in the chest wall (transthoracic pacing), or the electrodes may be introduced into the right ventricle by a catheter, usually passed into the heart via the jugular vein (transvenous pacing). Either technique usually provides excellent control of heart block and each has advantages to recommend it, but both also produce occasional complications.

Transthoracic electrodes require major surgery for installation. Transvenous electrodes may be installed under local anesthesia and shorten the patient's hospital stay, but the procedure requires a skilled catheterization team.

The wires to transthoracic electrodes appear to be subjected to greater stress by the incessant motion of the heart and so may be more likely to break. The electrodes themselves also become surrounded by scar tissue, a poor conductor of electricity that may seriously interfere with impulse transmission to the heart-muscle fibers. Transvenous electrodes may also become surrounded by scar tissue and, being less securely anchored, are more likely than implanted electrodes to pull away from the ventricular wall, with loss of pacing. Further, unless the installation is done skillfully, there is some danger that the catheter may perforate the wall of the right ventricle.

Current clinical practice apparently favors the transthoracic approach for younger patients whose condition is good enough to make chest surgery nonhazardous, the transvenous approach for older or more debilitated patients in whom such surgery might be risky.

CONCLUSION

During 1966 the programs of research conducted and supported by the National Heart Institute continued to enrich the store of fundamental knowledge of the cardiovascular system and the diseases that affect it and to yield new or improved techniques for the prevention, diagnosis and treatment of cardiovascular disorders. Findings stemming from these programs were disseminated in more than 3,800 papers and abstracts on every conceivable cardiovascular topic published during the year by NHI scientists and grantees. The brief summaries presented in this report represent only a very small sampling of those findings.

DENTAL DISEASE

DENTAL CARIES

Epidemiology.—People in the United States like to think this country has the best of health. Yet a 1966 grant-supported study at the Contra Costa County Health Department, California, showed that 3,900 five-year-olds had marked dental inadequacies. The children were divided according to parents' income into five socioeconomic groups. Only 29.6 percent from the highest income families were caries-free. Yet 18 percent of these more affluent children had never been to a dentist. In the lowest economic group, only 17.5 percent were caries-free and 52 percent had never been to a dentist. The children from homes with no more than $3,000 annual income had an average of 4.83 decayed, indicated-for-extraction, previously extracted, or filled teeth. Those from families with incomes over $8,000 had an average of 2.87 such teeth.

Clarifying the prevalence of caries, such surveys underscore the need for research to develop more effective means to control tooth decay.

Frequency of eating.—There is considerable evidence that tooth decay increases with frequency of eating, which, in part, might account for the high rate of caries among children and teen-agers. It would be helpful if snack food could be developed that would fight decay while satisfying between-meal hunger.

Grant-supported research at the University of Texas shows that feeding hulls from oats and rice or shells from peanuts and pecans retard tooth decay in mature rats. Moreover, if this regime is followed in early life, it gives long-lasting protection even to teeth that erupt after this type of feeding is stopped.

Since sterilizing hulls with heat reduces their effectiveness against decay, efforts are continuing to isolate the factor that gives them this ability, and to find another way to clean the hulls.

Effect of fluoride.—Evidence of the value of fluoride in reducing caries continues to mount. Collaborative X-ray diffraction research by Dental Institute scientists has now added proof that increasing perfection of tooth crystals occurs with increased fluoride content of enamel, and that teeth continue to incorporate fluoride after maturation. Since more perfect crystals are less soluble to acid attack, this research suggests that fluoride reduces caries by increasing tooth crystallinity.

In another Institute-supported study in Israel, it was shown that the amount of calcium in bone and tooth ash of human fetuses increases with the amount of fluoride in the water consumed during pregnancy, whereas the amount of phosphorus remains unchanged. Since it is well established that bone and tooth mineral are more soluble in acid and accordingly more prone to decay when the proportion of calcium is lower than normal, this investigation suggests that fluoride also acts to reduce decay by increasing the ratio of calcium to phosphorus in bone and teeth.

This same study also demonstrates that the amount of fluoride found in the fetal bones and teeth remains the same whether the water contains 0.5, 0.6, or 1.0 parts per million. Apparently, there is a maternal regulating mechanism to control the embryo's direct metabolism of fluoride.

A new method of topical application of fluoride shows great promise as a practical, effective means of reducing tooth decay. In Cheektowaga, New York, field trials with school children have demonstrated an 80 percent reduction in the amount of caries expected in places where fluoride in the water supply is too low for protection against tooth decay.

A jelly-like material containing 1.1 percent sodium fluoride was applied to specially fitted plastic mouthpieces, similar to athletic mouthguards. The children wore the devices for only six minutes a day during the school year. Be-

cause one dental hygienist is able to supervise several hundred children effectively, less dental manpower is required than in current methods of topical application of fluoride.

Among those children using the fluoride gel, baby teeth shed during the tests proved to have much more fluoride than those from the non-treated group. Moreover, many children with rampant caries at the outset developed no caries in the course of the two-year test. Urinalyses during the test period showed no increase in fluoride excretion, an indication that the fluoride remained in the teeth.

White spots.—Tooth enamel may sometimes develop white spots, which often become cavities. Dental scientists are trying to find out how enamel that is so affected differs from normal enamel, and what makes it vulnerable to decay. Indications that plaque, a film deposited on teeth by bacterial action, is not only acidic, but may also develop an electric current, have led grant-supported scientists at Tufts University to apply similar minute currents to blocks of dental enamel. White spots like those in living teeth quickly developed.

Because electrical potentials attract oppositely charged ions from considerable distances, it would be reasonable for positively charged calcium ions in enamel to be disturbed by this nearby electrically charged environment. Such electrolytic effects could increase the chemical effects of acids in breaking down enamel.

PERIODONTAL DISEASES

Bone resorption.—Advances made in the laboratory are pointing the way to improvements in treating diseases of the tooth-supporting tissues. Damage to these gum and bone structures accounts for most of the loss of teeth after middle age. As the condition progresses, bone resorption becomes a serious problem.

Tissue culture studies conducted at the Harvard School of Dental Medicine have shown that bone resorption can be inhibited by exposure to sodium fluoride. When parathyroid extract is introduced into a culture system, bone resorption occurs. However, this resorption is inhibited when the bone is first dipped into a sodium fluoride solution for periods as short as one minute, thoroughly rinsed and then exposed to the hormone.

Because such short exposure to fluoride is beneficial *in vitro*, scientists suggest the possible value of treating localized bone resorption due to chronic destructive periodontal disease by means of topical and applications of sodium fluoride in cases of gingivectomy and pocket removal in which dentin and bone are customarily exposed.

Bone metabolism.—A new hormone that lowers calcium levels in blood was first found in rats in 1963, and later in other animals. This hormone called thyrocalcitonin, has now been recovered from human thyroid glands obtained at autopsy by Institute-suported scientists while working at Rice University, Texas. In assays of activity, this purified hormone reduced calcium in rat plasma 10 percent.

Patients with several thyroid diseases were also studied. In one case of apparently defective parathyroid gland activity (pseudohypoparathyroidism), the amount of thyrocalcitonin exceeded the normal level 100 times, while in several cases of enlarged and tumorous thyroids it was not possible to detect any thyrocalcitonin activity.

The research points to a new role other than control of metabolic rate for the thyroid gland, and suggests that the hormone is extremely important in normal human physiology and metabolism of calcium. For example, the hormone from the parathyroid is known to make bone in tissue culture resorb. Grant-supported investigators at Harvard find that thyrocalcitonin can counteract this effect in the laboratory, and present evidence that the new-found hormone acts directly on bone.

Following these leads, many former studies of the thyroid gland and its effects on tooth formation and eruption, and on bone development must be re-examined. Also, the availability of an agent which can lower blood calcium might, after extensive experimental studies, prove useful for treating disorders of calcium metabolism.

Bacterial effects.—In one study on the causes of periodontal disease, the tissue destructiveness of waste products formed in the mouth by bacteria has been under investigation. When gum and corneal tissues of anesthetized rabbits were bathed continuously with dilute solutions of non-alkaline ammonia, the first bacterial product studied, they developed signs of damage. The corneas grew somewhat

opaque, and microscopic examination showed some loss of carbohydrate and some cell destruction in both tissues. Bathing without ammonia caused no damage.

Collagenase.—It is known that in periodontal disease, large amounts of collagen are lost as destruction of connective tissue progresses. This year Dental Institute scientists found a collagen-destroying enzyme produced by cultures of human gingiva. Cultures of gum tissue from patients with periodontal disease destroy collagen gels on which tissues are grown. The collagenase, found in the absence of bacteria, is destroyed by heat, and is released by living cells into the surrounding culture medium. The scientists believe that this calcium-requiring enzyme, which functions under normal conditions of health, may become excessively active and participate in the destruction of collagen during the course of periodontal disease.

Apparently this collagenase is also a factor in neuromuscular diseases involving collagen. It is frequently found in skin cultures from patients with amyotrophic lateral sclerosis, myasthenia gravis, Parkinson's disease, progressive spinal muscular atrophy, myotonic dystrophy, and toxic polymyositis. Steroid therapy seems to inhibit collagenase activity.

It is possible that the normal turnover of collagen is due to this enzyme, but that certain diseases upset the balance of control so that detection of excess enzyme becomes possible with the methods used.

BIOMATERIALS

At Brown University plastic teeth implanted in baboons for study periods of five years continue to be retained with effective function under biting stresses far beyond the usual level of human biting forces. Histological studies of cells in surrounding tissues show only slight differences between those enclosing the natural teeth and those around the artificial ones made of polymethylmethacrylate. Nontoxic and insoluble in water, this plastic is most promising as an implant material.

Dental scientists continually search for a direct plastic filling material which will harden quickly at mouth temperature, maintain a suitable color, and bond tighty to enamel and dentin in the presence of moisture. Such a substance would save time and money, and eliminate loss of sound portions of the tooth now removed to provide mechanical locking of the restoration. Progress towards the development of an improved plastic material for restoring anterior teeth has been made through American Dental Association scientists working at the National Bureau of Standards with grant support from the National Institute of Dental Research. Several silane-type bonding agents, when applied to teeth prior to filling, promise to improve the adhesion of unfilled resins and of resins with silica particles added to increase hardness and reduce shrinkage.

One of these silane coupling agents has proved suitable for directly bonding porcelain teeth to a plastic denture base without requiring a metal pin or other locking mechanism. This bonding will improve denture strength and esthetics, and also oral hygiene, since no bacteria or fluids can seep between the artificial tooth and the denture. Moreover, direct bonding in dentures, by eliminating the need for precious metals and reducing manufacturing costs, should result in savings estimated at eight million dollars a year.

New approaches have also emerged from the workshops on adhesive restorative dental materials sponsored by the Institute's Biomaterials Research Advisory Committee. In the proceedings of the second workshop, reported in 1966, PHS Publication No. 1494, findings were described that turned the attention of the Institute to studies of natural cements produced by marine plants and animals, such as the barnacle. The natural cements form as a liquid, harden under water, endure wide temperature changes and heavy stresses, last for years, and attract minerals from sea water so that the attachment area increases with time although the original amount of cement secreted was small. If such cements can be analyzed and the principles of the mechanism by which they harden under water explained, it should be possible to make similar substances suitable for filling teeth permanently. A recently established ad hoc committee is currently developing plans to set this new program in motion.

SALIVARY STUDIES

Regeneration of atrophied glands.—Stones in salivary glands can lead to the wasting away or atrophy of the gland. A surgeon treating a patient with salivary stones must decide whether to remove the obstruction or tie off the duct. The

latter procedure, a minor surgical treatment, might be preferred to the more serious operation of stone removal if the atrophied gland is unable to regenerate.

Scientists working under Dental Institute grant support at the Walter Reed Army Medical Center report that the salivary gland in rabbits can regenerate quickly after acute atrophy. The scientists blocked the rabbit salivary gland by tying the duct for three or seven days, and then removing the binding. Examinations showed that atrophy was well advanced after three days. However, after the removal of the obstruction, the glands began to recover within one day. Regeneration of the gland in the rabbit could mean that the human gland has similar capacities.

Role of saliva.—A sort of step-child among body fluids, saliva has been much less studied, though as accessible as urine, and more so than blood. It is more difficult to work with partly because it is the product of three main glands, and hundreds of smaller ones, which do not produce identical secretions. Accordingly, it is hard to collect in an uncontaminated state. Moreover, it does not keep well; warmth destroying certain properties and cold, others.

Nevertheless, it is a most important factor in oral health. Saliva affects mouth comfort and taste, contains a blood-clotting factor, responds to various hormones, and plays a role in mineralization of tooth enamel and in controlling the microbes in the mouth. When there is insufficient saliva, dental decay increases dramatically. Saliva also is necessary for dentures to adhere properly.

Indicator of body chemistry.—Dental scientists are convinced that if the components of healthy saliva were known and the normal ranges of the amounts of each were established, saliva, like blood, could be a useful indicator of some aspects of health. Thus, if too much or too little of certain of these substances could be demonstrated, diagnosis of some diseases might be made more readily.

At Hahnemann Medical College and Hospital in Philadelphia, an Institute-supported scientist is studying relationships between the sympathetic nervous system, which carries impulses to glands and smooth muscles, and salivary secretions. He finds it possible to alter the chemistry of saliva from submaxillary glands in animals and humans with guanethidine but not with other drugs known to block specifically the nerve fibers of the sympathetic network. He reports that this drug temporarily improves the chemical balance of organic components of submaxillary gland saliva in children with cystic fibrosis without changing the levels of calcium, sodium, or potassium. It is an unusually large proportion of nitrogenous compounds and certain enzymes which gives their saliva its characteristic cloudiness.

Calculus formation.—Saliva also plays a role in the formation of calculus or tartar, a hard, mineralized substance which forms at the base of teeth and is believed to be a major contributor to periodontal disease. A problem, however, arises in separating the effects of saliva on calculus formation from those of diet, heredity, and microbes. There is evidence that these three interacting factors, which are known to affect dental decay, are likewise very important in peridontal disease.

In humans, high rates of calculus formation are associated with high concentrations of protein in the saliva. Experiments with rats demonstrate hereditary effects: some strains fed unbalanced diets tend to form calculus even in germ-free environments; others rarely have calculus under any circumstance. Normally, rats on balanced diets are fairly calculus-free.

In collaboration with others, Institute investigators report that the composition of rat saliva varies between substrains of a single type of rat when both eat the same diet, and also varies further on different diets. Some rat types produce more calculus on high-fat diets and others on high-protein diets, but all have more protein in the saliva when forming calculus.

Genetic factors.—Only recently have scientists learned that people may inherit different types of salivary enzymes just as they inherit different types of blood. If variants of one salivary enzyme could be identified and grouped, as blood types are, the different groupings might be useful in studies of population genetics, and also serve as indicators of pathological conditions or of some hereditary diseases.

The enzyme which starts the digestive process as soon as chewing mixes food with saliva, is amylase, the chief enzyme in saliva. It converts starch into sugar. At first it was thought that amylase from saliva, liver, and pancreas was one substance, but as analytic techniques have improved, amylase has become the name for an enzyme family whose molecules differ in different parts of the body. It is now known that insect and mammalian amylase variants are inherited.

Moreover, Institute scientists who have purified salivary amylase and crystalized it, find that when redissolved, it also appears to have more than one molecular form. To prove this, they have used as an amylase separator, a tube filled with a clear plastic (a polyacrylamide gel column). When salivas from the parotid glands of people and rats are forced by an electric current to pass through the gel, the different amylase fractions move at different speeds. After the current is stopped, the gel with its layers of trapped molecules is laid on a starch-coated glass plate. All the varieties of amylase present destroy the starch but at different rates, leaving bands on the glass—a record easy to compare with that of other salivas.

The investigators find that saliva from each individual always produces the same pattern. So far, they have found five to eight different kinds of parotid amylase in each person. Also they report that parotid salivia amylases in rats differ from human ones. When animal and human salivas are mixed, the amylases can be separated and identified by this procedure.

With the aid of this disc-electrophoresis method, the scientists hope to learn more about human heredity, and its relationships with various oral and systemic diseases.

Dental Institute researchers recently found that people who cannot taste phenylthiocarbamide (PTC) have approximately 28 percent more dental caries than tasters. About 70 percent of Caucasians can identify, even when greatly diluted, the bitter taste of PTC, and 30 percent cannot. This ability to taste is an inherited dominant trait. Non-tasting is its recessive counterpart. When the tongue is cleaned of saliva, and PTC is dissolved in distilled water and applied there is no taste. Also, if a taster's saliva is mixed with PTC and then applied to a non-taster's tongue, it may sometimes be tasted. Salivia obviously influences taste.

DENTURE RELINERS

Institute-supported investigators at Ohio State University warn that people who use do-it-yourself denture reliners can do themselves serious harm. Improper pressures from such self-treatment can result in severe bone loss. Indeed, so much bone may be lost that both construction and wearing of dentures become most difficult.

Another danger of treatment without professional supervision is that oral cancer may go undetected. Because one of the last signs of oral cancer is pain, malignant changes may occur but not be discovered in the early stages when treatment is most successful. Earlier research has shown that the ill-fitting denture is an important factor associated with or predisposing to mouth cancer.

TEMPOROMANDIBULAR JOINT RESEARCH

In cases of children with injured, diseased, or congenitally defective jaw bones, surgeons have to consider whether an operation to restore function may not prevent the normal growth of the lower jaw. Preliminary experiments using bones transplanted from elsewhere in an animal's own body have shown that, under favorable circumstances, it is possible to replace the hinge of its jaw and still have growth continue.

Institute-supported surgeons at the University of California now report that children born without the hinge or condylar process of the jaw, may be greatly helped by transplants of bone growth centers taken either from their own rib junctions or from the head of one of the leg bones. In four carefully followed cases, the children are now able to open their mouths, chew better, have improved appearances, and their jaws have grown in the course of a two-year period. Moreover, the bone from which the autograft was taken has regenerated, and no loss of its function has occurred.

FEVER BLISTERS

Fever blisters, the most common of mouth sores, are caused by the herpes simplex virus. These sores are particularly annoying when they recur frequently, sometimes as often as every week or even daily. Immunologists long have wondered why repeated infections often occur even when the patient has in his blood a good supply of neutralizing antibody against this virus.

Now Dental Institute scientists have shown that, in the test tube, herpes simplex can exist in the form of an infectious virus-antibody complex (sensitized virus), and that this complex is relatively resistant to neutralization by anti-

body to herpes. These findings suggest that virus sensitization may be an important factor contributing to the chronic nature of certain viral infections. Recently, these scientists have succeeded in neutralizing the sensitized virus *in vitro* by the use of an anti-gamma globulin.

DENTAL PULP STUDIES

Tooth pulp usually reacts to injury by forming reparative dentin. This new dentin, if it is thick enough, provides an excellent protective barrier against mouth chemicals and dental filling materials because it lacks the tubular structure of the original dentin. Many dentists customarily use temporary fillings for several months before completing crowns and inlays in the hope that reparative dentin will seal the open ends of those dentinal tubules freshly cut in the preparation of the cavity.

Recently, clinical scientists at the Dental Institute found that properly used, high-speed cutting techniques of modern dentistry are so non-irritating to tooth pulp that inflammation is greatly reduced. For example, with some cutting procedures no reparative dentin formed even after six months, and with others, only a third of the teeth examined formed any dentin after 43 days. In fact, dentin seldom appeared before a lapse of 30 days, and then its daily rate of deposition was so small that even three months later there was not enough to make a reliable seal. Obviously, without a sufficient stimulus of injury, formation of reparative dentin is unpredicable, and when it does occur, is minimal. For this reason the investigators consider that it is impractical to put in a temporary filling and expect that a particular tooth will have formed reparative dentin three to nine months later. Rather, it is recommended that cavity liners and sealers be used as an adjunct to immediate repair of teeth.

ARTHRITIS AND METABOLIC DISEASES

RHEUMATOID ARTHRITIS

Rheumatoid arthritis has been described as a disease of man's supportive tissue system. It apparently cripples by destructively attacking the vast network of connective tissue that holds the body together. Although the cause has not yet been found for this, one of the most puzzling diseases of medical science, investigators are encouraged by recent evidence suggesting that the mycoplasma—microorganisms with characteristics halfway between bacteria and viruses—may be directly or indirectly involved in the etiology of rheumatoid arthritis.

Other factors that have been thought to be associated in some way with the onset of rheumatoid arthritis are heredity and emotional stress. NIAMD-supported investigators have now obtained evidence from a study of rheumatoid arthritis in twins that the onset of the disease is determined by factors occurring in the course of psychologic stress. In eight sets of identical twins (all female). in which only one twin in each set was affected, it was found that the affected twin had undergone a series of life events that were demanding and restricting, during which time she developed her first symptoms of rheumatoid arthritis. The unaffected twin, in every case, had no comparable experience.

Further information related to rheumatoid arthritis was obtained in a basic research study completed by grantee investigators. Their study of albumin metabolism in selected rheumatoid arthritis patients not undergoing treatment has indicated that low serum levels of albumin frequently encountered in such patients are associated with an increased turnover rate of albumin, indicating increased albumin catabolism rather than diminished synthesis. This finding is important because it is known that corticosteroid drugs, which are sometimes administered for rheumatoid arthritis, can further deplete reduced body pools of albumin and, thus, may be deleterious to a patient who is already chronically ill.

Another grant-supported study has helped to explain the anti-inflammatory and fever-reducing effects of aspirin, used much more extensively than corticosteroid drugs in rheumatoid arthritis and other arthritic disorders. This finding concerns lysosomes, subcellular packets of enzymes found in large numbers in synovial lining cells of rheumatoid joints. It had been shown previously that disruption of these lysosomes induces in rabbits an arthritic lesion similar to rheumatoid arthritis in man. Aspirin has now been found to stabilize lysosomes, suggesting that the drug's beneficial effects may be brought about by a lysosomal mechanism.

Another group of investigators has reported a study which offers hope for an effective form of therapy in rheumatoid arthritis and, possibly, in other diseases caused by faulty immune mechanisms (autoimmunity). They produced adjuvant arthritis (an experimentally induced form of arthritis exhibiting a true, but transitory, immunological reaction and polyarthritis symptoms) in rats. Treatment of these rats with rabbit anti-lymphocyte serum successfully suppressed the usual arthritis reactions in these rats; in contrast, untreated control animals all developed marked polyarthritis. This important research lead is being followed up with additional studies to determine its possible applicability to treatment of human arthritis.

OSTEOARTHRITIS

During the past year several significant findings have been reported by Institute-supported scientsits regarding osteoarthritis, a common disorder of unknown etiology associated with degenerative changes which alter the mechanical structure of the joints. Investigators at the Medical College of Georgia reported that *Rumalon*, a cartilage-bone marrow extract, is of clinical value in the treatment of osteoarthritis. The cartilage of patients with this disorder is thought to be deficient in chondroitin sulfate, a component of the ground substance of tissues. Thus, a drug capable of stimulating the synthesis of chondroitin sulfate in the affected tissues theoretically would be considered helpful in counteracting the pathologic changes in osteoarthritis. The scientists reported that *Rumalon* stimulates the uptake of radioactvie sulphur in human osteoarthritic cartilage, indicating increased synthesis of chondroitin sulfate. This study warrants further investigation of the basic mechanism of action of this extract, as well as continued clinical trials of its effectiveness.

RESEARCH ON JOINT DEVELOPMENT AND FUNCTION

It has been suggested that contractions of the skeletal muscles may play a role in the development of joints during the embryonic stage. Previous investigations of this theory, however, have failed to preserve the exact embryonic environment and, thus, the resulting joint deformities could not be attributed solely to the absence of movement. A study completed by scientists of the NIAMD and the National Institute of Child Health and Human Development (NICHD) has now shown that joints do not develop normally in check embryos which have been paralyzed experimentally. Abnormalities of joint development were found in embryos paralyzed by three different techniques. Joint cavities failed to develop and became filled with fibrous tissue which eventually bound the joint elements together, and joint surfaces were flattened and distorted. Results of the study clearly indicate that embryonic movement plays an important role in normal formation of joints.

In another study some biochemical and biophysical aspects of joint stiffness were clarified by a grantee investigator at the University of North Carolina. It is generally know that even temporary immobilization of normally movable joints can result in a permanent loss of motion. It is also appreciated that immobilization of joints surrounded by edematous soft tissue often produces joint stiffness more quickly and severely than immobilization of nonedematous extremities. The actual mechanism, however, by which range of motion is lost and the exact changes in joint structures which are responsible for decreased mobility are unknown. In this study, the investigator found gross, microscopic, and biochemical evidence that new collagen synthesis is the fundamental process in the pathogenesis of joint stiffness. The study also showed that surgical removal of newly synthesized collagen from strategic areas around stiff human interphalangeal joints produces immediate relief of flexion contractures. Long-term results, however, of surgical removal of excess collagen from stiff joints have not been satisfactory, it was concluded, because of subsequent collagen synthesis during the healing process.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a grave inflammatory connective tissue disorder which affects organs of the body in varying combinations. Although its cause is not known, evidence points to an abnormal antibody reaction. Circulating antibodies that are capable of harming the body's own tissues have been found in SLE patients. It has been suggested also that these antibodies may combine with the products of tissue breakdown to form immune complexes

potentially harmful to other organs such as the kidney. NIAMD-supported investigators have now found further evidence to support this theory. They have detected antinuclear antibodies in the skin lesions of SLE patients, and have proposed that such lesions may contribute to the formation of immune complexes capable of damaging other organs.

The study of a human disease is always greatly facilitated when an experimental animal model is available. Until 1961, when a strain of hybrid New Zealand mice was discovered to develop spontaneously a disease resembling human SLE, there had been no animal model. Further studies of these animals by NIAMD grantees have now provided additional evidence of the close similarity between this model and the human illness. The findings include typical LE cells, antinuclear antibodies, hemolytic anemia, proteinuria, and nephrosis with kidney failure—all of which are associated with the human disease. The incidence and severity of the lesions were much more prevalent in female than in male mice, a finding also consistent with human SLE. Further investigation of the model might provide clues to SLE's cause and development, lead to controlled studies of various methods of treatment, and provide a better understanding of the human disorder.

DIABETES

Diabetes mellitus is a complex disorder for which there is no known cure, and which ranks high on the list of diseases that cause death. This disorder affects individuals predisposed to it by their hereditary background. The most obvious defect in diabetes is the body's inability to metabolize carbohydrates normally. As a result, the diabetic is unable to utilize efficiently all of the carbohydrates he consumes and either to turn them into heat and energy needed for normal body functioning or to store them in the form of glycogen. Instead, the carbohydrates, converted into glucose, accumulate in the blood and are excreted in the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with derangement in the metabolism of fats and proteins. In its severe form, diabetes rapidly progresses to a state of grave metabolic derangement, called keto-acidosis, which may result in coma and death unless controlled by insulin administration.

It has recently been proposed that the basic cause of diabetes may be the production of a structurally abnormal insulin. This concept has gained support from an Institute-supported investigator who has shown that insulin isolated from the blood of diabetic children is significantly more resistant to destruction by an insulin-specific enzyme than is insulin derived from normal individuals. His finding suggests that there might be a genetically determined structural difference in juvenile diabetic insulin which contributes importantly to the underlying biochemical disorders of diabetes.

Institute scientists are continuing their studies of the Pima Indians of Arizona, a population group found recently to have the highest rate of diabetes ever reported. The investigators' most recent findings indicate that the effects of child bearing do not account for the higher prevalence of diabetes among women. Contrary to expectations, the prevalence of diabetes, especially in the younger age groups, was found to be somewhat higher in Pima Indian women who have not borne children than in those who have borne seven and more. The NIAMD scientists suggest that in previous studies which linked diabetes to pregnancy there was more likely an indirect association with obesity.

Diabetes resembling the human *maturity-onset* type has been described previously in hamsters, dogs, and the Egyptian sand rat. Institute-supported investigators now have described a metabolic disorder closely resembling human *juvenile* diabetes which has appeared as a new genetic mutation in inbred mice. The diabetic animals exhibit a severe disease syndrome with onset at an early age and a shortened life-span. Because the disease closely resembles juvenile diabetes in man and is readily reproducible, the new strain of mice will provide a much needed experimental animal model for further research.

The single most important action of insulin is to facilitate the entry of glucose into the cells of the body. An understanding of the precise mechanism by which insulin accomplishes this task is essential to full solution of the diabetes problem. It has been postulated that insulin may act primarily by initiating a disturbance at the cell surface which produces widespread structural changes of the cell membrane. Such changes, it is theorized, would lead not only to increased penetration of glucose and other substances into the cell interior, but might also explain several other known effects of insulin.

This hypothesis has been strengthened by scientist-grantees in New York and in Baltimore. The New York investigators have shown that radioactive insulin binds largely to the boundary membrane of the muscle cell. They have suggested that this action of insulin may facilitate the entry of glucose, electrolytes, water, and amino acids into the cell via a hormone-sensitive, possibly contractile, system which might also account for the known effects of insulin on protein synthesis.

The Baltimore scientists have lent credence to this proposal by showing that insulin has an *immediate* effect on potassium and sodium movement in and out of rat muscle tissue. This finding implies that insulin acts on the surface of muscle cells and supports the proposal that it acts primarily on the cell membrane.

It has been generally accepted that abnormal carbohydrate metabolism is the initial manifestation of clinical diabetes and that the small blood vessel abnormalities of the disorder which are responsible for some of its severe complications, develop only subsequently, as the disease progresses. Institute grantees have recently reported a very significant finding in prediabetic individuals—persons having two diabetic parents and genetically destined to develop diabetes sometime during their lives, who do not display as yet any chemical aberrations of the disease. These investigators were able to demonstrate that significant small blood vessel disease in muscles, expressed in the form of marked thickening of the basement membrane of capillaries, which is characteristic of overt diabetes, appears in at least 50 percent of genetically prediabetic subjects *prior* to the onset of carbohydrate abnormalities and in practically all diabetic patients thereafter. These findings suggest that small blood vessel basement membrane thickening may represent the primary lesion of diabetes, followed only secondarily by carbohydrate derangements. The significance of this observation is that diabetes investigators are now afforded a new angle of attack, a direction for research efforts which may be much more fruitful in determining the fundamental cause of diabetes than previous studies directed mainly toward the abnormality in carbohydrate metabolism.

Another complication of diabetes, diabetic neuropathy, is a condition characterized by pathological changes in the peripheral nervous system. It has been reported to occur in four per cent of diabetic patients, but is thought to occur much more frequently. The basis for such lesions has not been established. An Institute-supported investigator has now obtained evidence to suggest that a little-known chemical pathway involved in sugar metabolism is overactive in nervous tissue such as the sciatic nerve and spinal cord of diabetic rats. The existence of such a hyperactive mechanism in the nervous tissue, coupled with the marked accumulation of its products in diabetes, may have major implications in the development of diabetic peripheral neuropathy.

Idiopathic edema is a term used to describe localized or general swelling, associated with accumulation of fluid in certain body tissues, the cause of which is unknown. The disorder most often affects premenopausal women who are overweight, and emotionally tense and unstable. Studies of such patients now have suggested that idiopathic edema may be an early sign of latent, or mild asymptomatic, diabetes. Grant-supported scientists have found that these patients have both a small blood vessel abnormality and impaired carbohydrate tolerance, conditions which may precede the onset of clinically apparent diabetes. The investigators recommend that carbohydrate tolerance should be evaluated in idiopathic edema patients periodically, and treatment appropriate to the severity of any diabetic abnormality which may be found should be initiated.

CYSTIC FIBROSIS

Cystic fibrosis is an inherited generalized metabolic disorder characterized by the production of abnormal secretions by the various exocrine glands of the body. The disease is characterized primarily by malnutrition and lung disease. Although in the past cystic fibrosis was confined to the pediatric age group by its high mortality in infancy and early childhood, the disease is now recognized with increasing frequency among adolescents and adults. Recent studies have shown that there are far more adults than previously believed who carry a partial genetic endowment for the disease. The studies also have suggested that variants of cystic fibrosis may be responsible for some chronic lung and gastrointestinal disorders in adults usually not recognized as due to cystic fibrosis.

The basic defect underlying cystic fibrosis is as yet unknown and much of the research carried on by scientists of the NIAMD in Bethesda and by Institute grantees is devoted to discovering its nature. Institute scientists in Bethesda are

currently conducting intensive laboratory and clinical studies in an attempt to delineate further the chemical and clinical manifestations of cystic fibrosis and to uncover the fundamental defect responsible for the disease. Trials are also being made to ascertain the best type of treatment for the chronic lung involvement which is the major cause of death. The relationship of this disorder to other types of chronic lung disease and gastrointestinal disorders is also being explored.

Last year grantee scientists at Children's Hospital Medical Center in Boston devised a new, reliable diagnostic aid for cystic fibrosis which involves analyzing samples of toenails, fingernails and hair for elevated concentrations of sodium and potassium. The new test also proved useful in identifying adults who are carriers of the cystic fibrosis trait; at present there exists no uniformly reliable method for positive identification of such individuals. Furthermore, nail and hair samples, because of their ease in collection and storage, may be forwarded by mail, thus providing ready access to specimens which may be of diagnostic or genetic interest.

Just a few months ago an engineer at Washington University, Seattle, working in close collaboration with the Boston grantees, reported that by combining nuclear reactor techniques with fingernail clippings from 170 kindergarten children he could markedly accelerate screening of such children for cystic fibrosis. The new test involves irradiation of nail clippings from the toes or fingers in a nuclear reactor for about an hour. The amount of sodium in the nail clippings is determined by measuring the amount of radioactive sodium produced during irradiation. Sodium levels in the nails indicate to the researchers whether or not the danger of cystic fibrosis exists. As many as 400 specimens each day can be analyzed by this technique, as opposed to about 20 daily by conventional chemical assay. Only 0.1 mg of nail is needed for the reactor test, while the chemical method requires 200 times that amount. These investigators believe that the importance of early diagnosis in cystic fibrosis makes the test a valuable screening procedure for all admissions to a newborn nursery.

GASTROENTEROLOGY

This past year has seen several significant advances in the field of gastroenterology. These and other research findings are systematically uncovering promising leads and approaches in the search for improved diagnosis and treatment for the many afflicted with diseases of the gastrointestinal system.

In the search for an antipeptic agent for improved treatment of duodenal peptic ulcer attention has focused on the sulfated polysaccharides because of their interference with peptic digestion. An NIAMD grantee has shown that amylopectin sulfate is an effective antipeptic agent in the treatment of chronic duodenal ulcer. Initially, the investigator studied the effect of a single oral administration of amylopectin sulfate at five dosage levels. Then the effect of repeated administrations of amylopectin sulfate alone and in combination with propantheline bromide (an anticholinergic drug which inhibits gastric acid and pepsin secretions at their source) on gastric peptic activity was studied. Since amylopectin sulfate exerts no antacid or anticholinergic action, the grantee concluded that its inhibitory effect on peptic activity must be a direct one.

In a double-blind study of 60 patients with chronic duodenal ulcers conducted over a one year period to determine the long-term effects of amylopectin sulfate, propantheline bromide, and a combination of both, on the prevention of recurrences of peptic ulcer disease, it was found that patients responded significantly better on amylopectin sulfate alone or in combination with propantheline than they did on propantheline alone or on the placebo preparation.

In another significant investigation in this area, NIAMD-supported scientists have challenged present methods of antacid therapy for duodenal ulcer by showing that antacids have a surprisingly long effect on gastric acidity when given one hour *after* a meal. The current usage of antacid drugs in the management of duodenal ulcer is generally well accepted; however, the rationale for such therapy is based largely on results of studies in *fasting* duodenal ulcer patients, which have shown that antacids act for only 20 to 40 minutes (due to rapid gastric emptying), and that doubling the standard dose does not prolong neutralization. Now, in this study, the NIAMD grantees determined the effect of antacids on gastric acidity in duodenal ulcer patients following ingestion of a standard meal. Administration of a standard dose of antacid one hour after the meal depressed gastric acidity for at least three hours, while doubling the dose exerted an even

greater effect and prolonged the drug's action. The findings suggest that the conventionally accepted antacid studies in *fasting* ulcer patients should not form the basis for current principles of antacid therapy, and indicate that administration of antacids in reasonable doses one hour *after* a meal constitutes rational and effective duodenal ulcer therapy.

Last year, researchers supported by this Institute traced the cause of intolerance to milk in otherwise normal adults and in patients with inflammatory bowel disease to a deficiency of the intestinal enzyme lactase, which converts lactose ("milk sugar") into glucose and galactose. Evidence also was found that milk intolerance is a relatively common syndrome in adults. Other Institute-supported investigators now have shown that the milk intolerance syndrome is much more common in the Negro population than in the white, suggesting that intestinal lactase activity levels are genetically controlled. The NIAMD grantees suggest that environmental or selective fatcors in Africa may have played a role in establishing and maintaining low lactase levels as an inherited trait.

The etiology of malabsorption in patients suffering from intestinal scleroderma (in which the basic changes in the gastrointestinal tract are atrophy and fibrosis of the smooth-muscle coats) has long been the subject of debate. Malabsorption with intestinal scleroderma is characterized by abdominal distention and discomfort, vomiting and diarrhea. In this study by another Institute-supported grantee, three of four patients with documented malabsorption related to intestinal scleroderma responded dramatically to broad-spectrum antibiotics with remission of their symptoms and improved absorption. These research findings suggest the usefulness of this form of therapy and the possible role of bacteria in the pathogenesis of malabsorption in these patients.

In another area of gastrointestinal research, an NIAMD-supported scientist has obtained experimental evidence that a *blood-borne* mechanism, in addition to a direct, mucosal irritant factor, may be responsible for aspirin-induced gastric bleeding. There have been numerous clinical and experimental observations demonstrating a causal relationship between gastrointestinal bleeding and the ingestion of salicylate compounds. Previous investigations have shown a direct erosive effect of acetylsalicylic acid on the gastric mucosa. These latest findings, in which the investigators induced bleeding in isolated, denervated stomach pouches of dogs after oral administration of salicylates, have diverted attention to the ability of salicylates to cause gastrointestinal hemorrhaging by means other than direct mucosal irritation.

KIDNEY DISEASE

NIAMD interest in research of kidney disease includes the various specific kidney disease entities, kidney transplantation studies, improved understanding of chronic uremia—the end-stage of kidney disease—and development of better artificial kidneys. Progress, for example, in the latter category was apparent this past year when a group of Institute-supported investigators developed a new artificial kidney which is considerably smaller and more efficient than existing types. The new device costs half as much as the conventionally used Kiil dialyzer, can be assembled in ten minutes and can be sterilized in an autoclave. Being compact, it has decreased very considerably the presently high blood priming requirement and the need for compensatory blood transfusion. This new artificial kidney can cleanse a patient's blood in 8 to 10 hours, compared to the 12 to 14 hours needed with the Kiil unit; thus, the bed capacity of artificial kidney treatment centers can be increased considerably with the aid of the new device.

At the present time a series of these new artificial kidneys is being produced for extensive testing under routine operating conditions.

During this past year, scientists supported by the NIAMD have made significant contributions toward identifying and characterizing the toxic factors in uremia. Identification of these factors in the blood of uremic patients is essential to a better understanding of uremia and to improving hemodialysis apparatus and techniques.

Treatment of uremic patients with an artificial kidney usually results in clinical improvement, suggesting that the small molecules removed by dialysis contribute to the symptoms of uremia. Although other investigators have shown that metabolic processes are impaired by factors present in the serum of uremic patients, for the most part they have been unable to characterize such factors chemically.

Recent studies have suggested that catabolism of aromatic amino acids may lead to accumulation in the blood of intermediate products which may play a role in

development of the toxicity of uremia. Now it has been shown by NIAMD grantees that blood levels of aromatic amines (degradation products of aromatic amino acids) are markedly elevated in uremic patients, that these high levels are correlated with blood urea nitrogen levels, and that they are reduced significantly by hemodialysis with an artificial kidney, resulting in improvement of the patients' clinical status. These findings suggest that aromatic amines play a role in the toxicity of uremia.

In the area of kidney transplantation this past year in NIAMD-supported scientist markedly reduced early failure of kidney homografts by a program of "renal-protective" management. By hydrating living, consanguinous donors immediately before operation, the grantee has been able to reduce significantly early functional failures of kidneys transplanted from the donors. This program of "renal-protective" management was employed to offset kidney damage that begins with anesthesia and is worsened during subsequent surgical manipulation of the organ.

Another NIAMD grantee has been able to prolong survival of canine kidney transplants by treating recipient dogs with horse antiserum to dog lymphocytes. He has found that horse antiserum to canine lymphocytes prolongs significantly the servival of kidney transplants in dogs. Two of seven animals receiving such treatment before and after kidney transplantation have survived beyond 350 days with apparently normal kidneys and normal kidney function. The NIAMD grantee suggests that lymphocyte antiserum treatment might increase the effectiveness of immunosuppressive agents such as chemotherapeutic and corticosteroid drugs and might reduce the dosage required for maintenance of transplanted organs.

This past year, NIAMD scientists have reported on a host of findings shedding light on several diseases involving the kidneys. Among these is cystinuria, a disease characterized by urinary excretion of large amounts of the amino acids cystine, lysine, arginine, and ornithine, and by formation of cystine stones in the urinary tract, and thought to be caused by a hereditary renal transport defect. It has been suggested that cystinuria is due to more than one single inherited disease process, however, and NIAMD investigators recently obtained evidence of an intestinal as well as a renal transport defect in this disorder. In their report this past year, they describe results of *in vitro* transport studies with intestinal mucosa tissue, oral loading studies with cystine, and patterns of urinary excretion of cystine and dibasic amino acides in parents and children of the affected cystinuric patients. The findings resulting from these studies indicate that cystinuria encompasses at least three biochemically and genetically distinct defects.

In cystinuria, the kidneys fail to reabsorb the amino acid cystine. Since cystine is relatively insoluble, tiny cystine crystals may be produced in the urine and may accumulate in the kidneys, frequently leading to the development of kidney stones. Conventional therapy, including increased fluid intake, alkalinization of the urine, and dietary restriction of sulfur-containing amino acids is not always effective.

It is known that penicillamine, a degradation product of penicillin, can markedly reduce urinary cystine excretion and prevent new stone formation by reacting with cystine to form the more soluble penicillamine-cysteine complex. An NIAMD grantee now has shown that prolonged penicillamine therapy sharply reduces the size of existing cystine stones in the kidney and eventually dissolves them completely, without any serious side effects.

Chronic pyelonephritis, a slowly progressive kidney disease, is believed to result from the scarring effects of persisting and recurring bacterial infections. The disorder apparently occurs more frequently in diabetic patients than in other groups, but there is no unanimity of opinion as to the actual frequency of the disease in diabetic and in nondiabetic groups. Histologic and bacteriologic studies by an NIAMD grantee now have shown that there is essentially no correlation between the presence of positive urine cultures, positive renal tissue cultures, and the histologic diagnosis of chronic pyelonephritis in juvenile diabetic patients. These findings suggest that factors other than the continued presence of bacteria in the kidney play a role in the pathogenesis of chronic pyelonephritis.

HEMATOLOGY

The National Institute of Arthritis and Metabolic Diseases, through direct research in its Bethesda laboratories and through grant-supported studies, has made significant contributions to such blood diseases as hemophilia, purpura, and the anemias, among others.

This past year, an Institute grant-supported scientist reported a clinical finding of importance to the treatment of hemophilia. Approximately one patient in five with hemophilia will become sensitized to the therapeutically administered antihemophilic globulin (AHG), which is deficient in this disease, and acquire antibodies against this blood coagulation factor. Hemorrhage occurring in such patients, particularly in a vital area such as the throat, poses a difficult therapeutic problem. Considerable amounts of AHG-containing *human* plasma are required to stop the bleeding and such large amounts may overload the patient's circulation.

The grantee-scientist has reported controlling life-threatening hemorrhages in three such patients by infusion of potent concentrates of AHG derived from *animal* sources. The patients had failed to respond to conventional therapy with fresh frozen human plasma and death due to respiratory obstruction seemed imminent. Responses were dramatic in all three patients following infusion of *porcine* or *bovine* AHG concentrate. Marked improvement was noted within hours and all patients were symptom-free after five to ten days.

The potent animal AHG concentrates have been used to similar cases in England for several years, but have not been used heretofore in this country. Since repeated use of such agents may induce the body to form antibodies, they must be reserved solely for life threatening situations.

An Institute scientist in Bethesda, in collaboration with a scientist at the National Institute of Dental Research, has now shown that infusion of human AHG concentrate is the best therapy available for hemophilic patients undergoing oral surgery who would otherwise run the risk of uncontrolled bleeding. All final clinical results were excellent in seven hemophilic patients who underwent simple extractions of one to 11 teeth, or complex extractions of 17 to 31 teeth. Although their study proved this procedure to be feasible, it is also expensive, and the investigators are currently evaluating more cheaply prepared, but apparently equally effective, plasma fractions.

One Institute-supported scientist has shown that hemoglobin S-D disease, a condition in which the red blood cells contain two abnormal types of hemoglobin—hemoglobin S which is present in larger amounts in sickle cell anemia, and another variant, hemoglobin D, is a comparatively benign disorder which is often misdiagnosed as sickle cell anemia, a more severe blood disorder, but can be differentiated from the latter in a number of ways. Such a distinction is important because of the different prognosis in the two diseases.

HEPATITIS AND TRANSFUSIONS

An estimated 1200 patients die each year of acute hepatitis in the United States. The life of one patient with apparently fatal acute hepatitis has recently been saved, however, by Institute-supported scientists in Boston who employed experimentally massive exchange blood transfusions. This procedure, used as a last resort measure on two successive days, resulted in unmistakable clinical improvement within 48 hours, gradual recovery, and discharge from the hospital six weeks later.

It is noteworthy that a group of investigators in South Africa reported, almost simultaneously, similar successes with the same procedure in seven of eleven such patients. Although such an extreme measure as exchange transfusions should be reserved for hepatitis patients who do not respond to more conservative therapy, the gratifying result obtained by the Boston scientists justify further exploration of this form of therapy.

SHOCK THERAPY

This past year Institute scientists have reported on the completion of their 15-year research on burn shock, a condition which frequently accompanies extensive burns. The scientists, working with Peruvian colleagues in Lima where severe burns are commonplace due to the widespread use of kerosene stoves, have compared saline fluid therapy and plasma therapy in the treatment of burned patients. Their results have shown that oral saline solutions alone are as effective in the prevention and treatment of burn shock in adults and children as other more costly and less simple forms of therapy, and that addition of plasma transfusion to saline solution therapy offers no conclusive additional advantage.

For more than three decades intravenous infusion of plasma has been considered essential in the prevention and treatment of often fatal burn shock.

The rationale for this widely used fluid regimen is based primarily on the knowledge that there is a loss of protein, fluid, and electrolytes into the burned area, and that experimental removal of plasma (as well as electrolytes) produces death from shock in animals. In the study by NIAMD scientists the efficacy of isotonic saline solutions alone was compared with a saline-plus-plasma regimen in the early treatment of severely burned patients. Results indicate that adequate therapy with saline solutions has reduced shock mortality to a point where no further benefit can be gained by adding plasma infusions to the regimen.

ENDOCRINOLOGY

In attempting to understand any disease process or physiologic disorder it is necessary to consider the possible etiologic role of hormones and the factors which regulate the synthesis, release, and degradation of these hormones. The isolation, purification, characterization, and synthesis of hormones is proceeding rapidly, and the few remaining unidentified endocrine factors should succumb shortly to the latest technical advances of biomedical research.

Human growth hormone, which functions primarily to regulate body growth processes, has been used successfully in the treatment of hypopituitary dwarfism and related disorders. The demand, however, far exceeds the supply of the hormone, which is obtainable only from human pituitary glands at autopsy.

The chemical structure of this vital hormone was determined during the past year by a grantee-scientist at the University of California, who, ten years earlier, had first described the isolation and partial characterization of the same hormone. His most recent finding marks a major advance toward understanding the several modes of action of human growth hormone and increases the chances for its eventual synthesis in the laboratory.

It is anticipated that "core" fragments of the molecule may be characterized which retain specific biological effects, such as growth-promotion, mammary gland stimulation, and a fat-releasing effect. These fragments may be synthesized initially and, ultimately, the large, complex molecule itself may be made.

DERMATOLOGY

Much skin disease research in recent years has been focused upon psoriasis, a very widespread condition, and perhaps the most baffling of skin disorders. One important aspect of tihs research has concerned the evaluation of several potent anti-cancer drugs, with a view toward making them safe for use in the treatment of psoriasis. The beneficial effects of anti-cancer drugs such as methotrexate and aminopterin in psoriasis have been recognized for some time. The use of such potent agents, however, has been associated with a number of serious side effects.

Preliminary studies conducted during the past year by scientists receiving support from the NIAMD and the National Cancer Institute have shown that another anti-cancer drug, triacetyl azauridine, is markedly effective and relatively safe for patients severely disabled by psoriasis. Substantial improvement was seen in 14 of 15 patients who received prolonged treatment with the new agent, while a rapidly reversible, moderate anemia was the only significant side effect encountered.

It is well known that psoriasis may improve or worsen for no apparent reason. The investigators feel that the consistent beneficial results obtained with triacetyl azauridine, however, warrant more comprehensive clinical studies of the drug in order to establish whether it is safe and effective for psoriatic patients who have become resistant to other forms of therapy. Such long-term studies are currently being conducted by the investigators.

Other grantee-scientists in San Francisco have delineated the skin lesions which characterize ataxia telangiectasia, a serious and exceptionally rare disease of the central nervous system and skin, thus permitting its differentiation from several similar but more common disorders with which it may be confused.

NEUROLOGICAL AND SENSORY DISORDERS

INTRODUCTION

More than 200 diseases are known to afflict the brain and the sense organs. Best known to the public are the chronic neurological disorders such as cerebrovascular disease (stroke), epilepsy, multiple sclerosis, Parkinson's disease, brain

tumors, muscular dystrophy, cerebral palsy, and other brain-centered disorders which cripple millions of Americans. In addition, the disorders causing blindness, deafness, and other impairments of human communication are responsible for long-term disability.

Much remains to be learned about the intricate control network which the brain and nervous system form in the human body, directing all the automatic and voluntary functions. When any part of this master system fails to function normally, a neurological or sensory disorder may result. Finding the causes and prevention of malfunction or injury of the brain and nervous system, as well as understanding its normal processes, are goals of the National Institute of Neurological Diseases and Blindness.

Fortunately, over the years, research activities sponsored by the Institute have helped to discover the cause and prevention of some of the major impairments. Institute programs also have led to improved techniques of diagnosis and treatment.

An ever-increasing number of scientists and physicians are committed to conquering the disorders of the brain, nervous system, and senses. Some of the findings of investigators working in the Bethesda laboratories and at grant-supported medical institutions are summmarized in the following highlights of research.

Collaborative perinatal project

Scientists have long suspected that neurological and sensory disorders of childhood, including cerebral palsy, mental retardation, deafness, and epilepsy are associated with prenatal, natal, and postnatal damage to the nervous system. For this reason, the Collaborative Perinatal Research Project—a joint endeavor of 14 medical centers and the National Institute of Neurological Diseases and Blindness—was begun in 1959. This study was designed to determine the relationships between factors affecting women during pregnancy and the neurological and sensory disorders which may develop in their offspring.

In 1966 the Project passed a significant milestone with the birth of the last baby to be born to the more than 60,000 mothers registered by the 14 collaborating institutions. This event, which marked the end of the obstetrical phase of the Project, signaled the beginning of a period of intensive analysis of study results collected so far.

Although final analysis of all study data will not begin until 1974 when the information-collection phase of the Project is completed, important preliminary findings have been made available. Some of these findings were reported in the second scientific session of the Project held in 1966:

Prematurity appears to be the greatest single factor associated with birth defects. Whatever its cause, prematurity has a close relationship to neurologic damage. Only 7 to 10 percent of infants are classified as premature—either by a weight of less than 2,500 grams or by time of gestation. But these premature births account for 70 percent of neonatal deaths. Premature babies have three times as many abnormalities as normals.

Among the leading causes of prematurity are placenta previa, premature placental separation, and incompetent cervix. There is no known preventive for the first two conditions. But following surgical treatment of the incompetent cervix, a relatively recent obstetrical development, there is reduced fetal loss, increased neonatal survival rate, and reduced neurological abnormality.

A new and promising area of investigation is the possibility of predicting birth weight early in pregnancy to provide for changing the natural course of certain pregnancies. The birth weight of the infant appears to be the best gauge for predicting neonatal mortality and infant morbidity.

Project researchers used 37 variables to analyze data on some 6,500 women. More than two dozen of the 37 variables provided statistically significant simple correlations with birth weight. Smoking appeared to be a particularly important factor. Women who smoke a pack of cigarettes a day, for example, could expect to have a baby about 165 to 180 grams lighter than a baby born to the average nonsmoker. A history of hypertensive disease was also associated with a drop in birth weight. Altogether, investigators were able to account for 50 percent of the variability in birth weights, the highest correlation ever found.

A study of the association of maternal age and parity to pregnancy outcome reached a number of interesting conclusions. The best time for a woman to have a baby is between ages 20 and 27. The most successful pregnancies are the second and third. The most unfavorable pregnancy results are in very young (teenagers) and elderly mothers. The study also showed an unfavorable out-

come in women having too many pregnancies too soon, at 22 years of age or less. Early and frequent pregnancies were associated with an increase in neonatal mortality, prematurity, low mental scores, neurologic abnormalities, and anemia.

Another report on the Project revealed that a disease called congenital toxoplasmosis is more common than phenylketonuria, with an incidence of one in 2,000 births. NIH scientists tested serum specimens from 23,000 pregnant women for antibody to Toxoplasma. They found that 47 women had high titers or showed significant increases in antibody during pregnancy. The babies of these 47 women are investigated in detail. Five infants with growth abnormalities definitely had congenital toxoplasmosis. In ten other cases, the disease was suspected. Six of these had motor retardation, two were stillborn, and two died in the neonatal period. Efforts are now being directed toward determining the mode of transmission of toxoplasmosis, and means for its prevention and treatment.

Cerebral palsy

Cerebral palsy (CP), a brain-centered disorder affecting muscular control, is one of childhood's greatest cripplers, afflicting about 20,000 live-born infants in the United States each year. An estimated half-million people lack normal control of their muscles because of this affliction, which has its roots in harmful events that affect either the mother or child during the critical time from conception through birth.

Factors producing cerebral palsy and other forms of brain damage in infancy are becoming more evident through the important data acquired by the Institute's Collaborative Perinatal Project.

Because cerebral palsy is largely rooted in unfavorable events from conception through birth, accurate information must be acquired about occurrences to the mother or child during this crucial time. Project findings relating to possible causes of cerebral palsy in this period include data on virus infections, which are a potential cause of serious neurosensory damage to the fetus or newborn. For example, the impact of the nationwide rubella (German measles) epidemic, which produced 20,000 to 30,000 neurologically impaired babies, and the role of toxoplasmosis and cytomegalic inclusion body virus (salivary gland virus) have been further clarified. Other Project activities of significance to cerebral palsy concern pathologic studies demonstrating the role of brain hemorrhage in the newborn, and the development of further obstetrical guides to recognizing high-risk pregnancies.

For the thousands of children who are now handicapped by cerebral palsy, ways must be found to help them obtain the fullest use of their potential. Institute-supported neurosurgical teams are making hopeful strides in this direction. These surgeons, employing stereotactic methods, are creating carefully placed lesions in certain areas of the brain.

One group of investigators has noted encouraging results of their operations on a small number of selected children, in whom all other methods of alleviating their intense symptoms (hypertonicity) had failed. Most of these children had cerebral palsy. Following surgery in the cerebellar region of the brain, the children showed a marked decrease in movement disorders, diminution of stiffness, relief of intense pain caused by muscle spasms, and in general appeared easier to care for and capable of deriving enjoyment from life. One child, who had been severely incapacitated, was able to walk and to be graduated from high school.

Clinical results of this significant study were the outgrowth of years of experimental efforts to understand the interrelations of the various parts of the nervous system, particularly with respect to the motor centers which regulate movement.

Another grant-supported neurosurgical team utilized electrical stimulation to create therapeutic lesions in cerebral palsy patients. They implanted electrodes in a number of subcortical structures (striatum, thalamus, and mesencephalon) of the brain and correlated the effects of chronic stimulation in specific areas with the clinical picture. This information was then used to select the site or sites of the surgical lesion. Appreciable improvement was reported in at least one-third of the cases; the extent of improvement depended upon the area of the brain where the lesion was localized.

Inborn errors of metabolism

Certain diseases associated with faulty body chemistry can be accompanied by brain-damaging consequences unless preventive measures are instituted. In some cases of inborn errors of metabolism, the problem is attributed to missing enzymes which activate chemical changes in the body's use of food or hormones, and in other cases, the cause is overactive enzymes which lead to an excess of toxic compounds in the brain or other body organs.

Research is making it increasingly possible to identify the conditions associated with malfunctioning of body chemistry, thus paving the way to prevention of organic mental impairments and other lifelong damage.

This past year, the identification of an enzyme, lack of which leads to Gaucher's disease, and of a different enzyme, lack of which leads to Niemann-Pick disease (both forms of mental retardation), was made by a neurochemist of the National Institute of Neurological Diseases and Blindness. In a 1966 summary of medical progress on inborn errors of fat metabolism in an outstanding medical journal, he traced the chemical search leading to the finding of the cause of these two disorders.

The investigator's paper presents significant theories for future treatment, dependent on the outcome of future research. Among his theories for treatment is the synthesis in the test tube of the missing enzyme, and its regular administration to the patient, even as insulin is used for the lifetime of the diabetic patient. Another theory he presented is the possible future donation of a healthy spleen to replace a spleen which cannot produce the necessary enzyme. Still another theory he discussed is the future administration of an appropriate DNA or RNA to correct the error in the pattern of heredity of these children.

The mere proposal of such theories marks the tremendous progress in recent years in knowledge of donor-transplants of organs, and of information on the cell-patterning qualities of DNA and RNA. Publication of these theories is a challenge to further research.

The NINDB neurochemist also suggested that identification of an enzyme which causes an inborn defect may make possible tests for identifying those parents who are normal themselves, but carry both a normal gene and a defective gene for an inborn defect of metabolism. He made successful observations of tissue cultures from patients with inborn defects. This tissue culture technique may lead to one of the ways by which the heterozygous state (having both normal and defective genes) in the parents can be identified.

Institute grantees and a European investigator discovered the cause of a kind of mental retardation called metachromatic leukodystrophy (MLD). Lack of adequate amounts of an enzyme called sulfatase allows certain body chemicals to accumulate to the point where they damage the brain and kidneys. In fact, the grantees identified three forms of the enzyme, sulfatase A, B, and C; all were decreased in activity in a variant form of MLD, as published in 1966.

These grantees also found distinctive sulfatase abnormality in each of two patients with a form of mental retardation called gargoylism (Hurler's syndrome).

Also, this past year, a scientist supported in part by a Neurology Institute grant found three previously undescribed ketones in the urine of a patient with the form of mental retardation called hyperglycinemia. Further research seeks an explanation for the presence of these unusual chemicals.

Epilepsy

The convulsive disorders (epilepsy) affect an estimated one to two million Americans, with a higher prevalence among children than adults. Little is known about the cause, and there is no cure. However, seizures can be controlled in the majority of patients through the use of one or more anticonvulsant drugs. The Institute's epilepsy research program is concerned with what happens to the brain during a seizure, as well as understanding the seizure-producing mechanism, and with developing more effective methods of treating and eventually curing these disorders.

To better understand the seizure mechanism, scientists have attempted to produce seizures in animals. This past year, seizures closely approximating clinical epilepsy in man have been produced in laboratory animals by methionine sulfoximine (MSO). About 24 hours after receiving this compound, the animals exhibit spontaneous and repetitive seizures. Chemical studies of the brains of these animals, which may provide a clue to the seizure-producing mechanism in man, show alterations in the level of glutamine, a normally occurring constituent whose activities may be related to the seizure susceptibility of the brain.

Scientists have also developed a microtechnique for applying a chemical compound to a single neuron (nerve cell) in the brain and simultaneously monitoring the effects of the compound. With this technique, certain compounds have been used to produce seizure activity in the brain of a laboratory animal. Following this, various substances have been tested for effectiveness in halting the abnormal activity. Although this microtechnique has not yet demonstrated a control substance effective in arresting seizure activity, it has revealed that this activity is a "spreading" phenomenon. It may spread from the single treated

neuron to other untreated ones and result in a generalized seizure in the animal.

In one clinical study this past year, patients with sensory-evoked epilepsy (seizures triggered by visual or auditory stimuli) were taught to tolerate the noxious stimuli by a conditioning process. A computer automation program was devised which would present the stimulus—which might be a certain musical composition, a startling noise, or a type of light—in combination with a similar but benign stimulus or at a benign frequency. When the patients became insensitive to the stimuli (seizures were no longer produced by it), they were taught to reinforce the conditioning to maintain their own insensitivity. Physicians working with these patients were afforded the opportunity to study one of the rarer forms of epilepsy and to develop an effective treatment, if not a cure, for it.

Head injury

Today, 70 percent of the accidental fatalities in this country involve some form of head injury. The Institute's head injury research program is concerned not only with the immediate causes of injury but also with prevention and with the chain of events following injury. These events may produce swelling and increased pressure in the brain and cause damage to other body systems as well as to the central nervous system.

This year, laboratory studies have shown that a form of injury which can cause concussion and produce damage to the nerves, spinal cord, and brain, is whiplash. Whiplash describes the injury produced in a typical rear-end automobile collision when the body is thrown forward rapidly and the head snaps back then forward to follow the body's forward path.

Recent studies on whiplash and on the effect of impact to the head have aided in the design of more effective protective devices. A collar which reduces bending and stretching of the neck, but does not immobilize the head, protects against concussion caused by direct impact. A lap belt which restrains the body from falling forward in combination with a specially designed heardrest to keep the head from snapping back would appear to be most effective in protecting against whiplash injury. These findings are based on laboratory animal studies, which include neurophysiological, biochemical, behavioral, and metabolic studies. The research is being conducted by the National Institute of Neurological Diseases and Blindness in collaboration with the U.S. Department of the Navy.

The Institute's head injury program is concerned not only with the impact of injury but also with the chain of events following the injury. According to recent studies, the metabolic response to head injury appears to be similar to the response occurring after any bodily injury; however, it differs somewhat from responses to general surgery. Primary excessive reactions are disturbances in water balance and acid-base alterations. These reactions may cause water retention, dehydration, or respiratory difficulties which can affect the functioning of all body systems and directly influence the patients' chances for survival. These systemic responses are in addition to specific changes in the blood brain barrier which lead to brain swelling after injury.

Because of the growing research interest in trauma, a conference to review the entire state of knowledge in this field was held in February 1966, at the University of Chicago. Experts in neurology, neurosurgery, physiology, theoretical physics, and engineering gathered to formulate a multidisciplinary plan for attacking this critical problem.

Brain tumors

Little is known about the cause or prevention of brain tumors. The latest available statistics indicate that almost 8,000 persons die each year from this cause. It is estimated that the number of living cases with brain tumors may be as high as 500,000.

Certain tumors, because of their nature, can be completely removed by surgery; others, because of their location, their widespread growth throughout the brain, or rapid growth characteristics, cannot be helped by surgical techniques. In addition to developing greater surgical skills, Institute researchers also are attempting to perfect methods of drug administration to treat more effectively inoperable brain tumors.

Last year, Institute scientists found that a small reservoir implanted under the scalp, could provide a research method of treatment of brain tumors. The reservoir is used to hold the most appropriate known drugs for treatment of both adults and children with cancer in the form either of a brain tumor or of leukemia of the brain covering. The fluid is conducted through a tiny implanted tube to

the area of the tumor which cannot be entirely removed, or to the most appropriate brain space (ventricle) for patients with leukemia of the brain covering.

This enabled the physicians to bypass the so-called "blood-brain barrier" which protects the brain from harmful substances in the blood, but also keeps out some useful medicines. This barrier has made it useless to inject an antitumor drug into an artery, even a local one to the tumor area.

Now, while awake in the comfort of his own hospital room, the patient can be given an amount of the selected antitumor drug through the reservoir, as many times as seems wise. At the end of a day of "perfusion" of the drug into his brain, he can walk about and eat a full meal. While some improvement has occurred, as yet it has not differed significantly from that in comparable patients on conventional treatment. Scientists hope for better results with a new group of patients receiving a higher dose level of the best known drugs.

In research supported in part by a grant from the Institute, some patients with brain tumors have been made more comfortable by the use of corticosteroids, although the tumor itself was not attacked. The swelling of brain tissues by water saturation (edema) causes painful symptoms which may be more distressing to the patient than the direct effect of the tumor mass. By using corticosteroids, the Institute grantee reduced the brain swelling with considerable increase in comfort for the patient.

Multiple sclerosis and chronic degenerative disorders of the nervous system

Each nerve fiber within the body's vast network of nerves has a protective covering or insulating sheath made of a fatty substance called myelin. Multiple sclerosis (MS) is the most common of a group of disorders characterized by the destruction of myelin and excess proliferation of the supporting cells of the brain (glia).

Multiple sclerosis affects adults mainly in the age group between 20 and 40 years. As many as half a million Americans suffer from sclerosing disorders. Multiple sclerosis is usually chronically progressive, proceeding in a series of unpredictable attacks ultimately leading to long-term disability. In earlier stages, attacks are often followed by periods of remission. Neither the cause nor an effective treatment have been found. However, research studies of related sclerosing disorders and studies of large groups of MS sufferers are beginning to reveal significant patterns in the development and etiology.

This year, a clue was found which may help unravel the mystery of multiple sclerosis. A human neurological disease, kuru, was successfully transmitted to animals. Kuru, like MS, is a degenerative disease of the nervous system previously considered to have little to suggest an infectious process.

Researchers have taken tissue from kuru victims and injected it into the brains of chimpanzees and other animals. After almost 2 years, seven of eight inoculated chimpanzees developed symptoms almost identical with the human kuru disease.

This is a most significant event because medical researchers have long suspected that viruses may cause many baffling disorders of the human nervous system. It encourages the extension of similar studies to other chronic neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, Parkinsonism, and certain chronic encephalitides of children.

The study of disease patterns is another approach to research in the sclerosing disorders. According to an epidemiological study of 1,000 U.S. veterans, Americans with higher education and earning power are most susceptible to multiple sclerosis. The study also revealed that a larger number of veterans from the cities have multiple sclerosis than those from rural areas.

In this study, a closer look was taken at the disease as it occurs in northern climes. Previous environmental studies of MS indicate that more persons are affected in temperate climates than in warm, subtropical areas.

In another study, also on the epidemiological aspects of the disease, a higher prevalence of multiple sclerosis was confirmed in immigrants from temperate latitudes than in those from warm regions. The study also indicated that the onset of the disorder may be as long as 10 or 15 years after leaving the temperate climate for the subtropical area.

In this study, conducted in Israel, higher incidence rates were found in Europeans immigrating between the ages of 15 and 29 than in the youngest age group, those less than 15 years old. These data suggest that multiple sclerosis is acquired, at least in many cases, before age 15 years. However, it is unlikely that the disease is acquired at birth or in early infancy since migration from Europe to Israel before age 15 years appeared to have had a protective effect. However,

since such individuals are still at a relatively young age, further follow-up studies are required to verify this observation.

Neuromuscular diseases

Neuromuscular disorders, all of which involve weakness or paralysis of muscle, may result from malfunction of the nerve cell, the nerve-muscle junction, or the muscle fibers directed by the nerve cell. Malfunctions in this process are expressed in various neuromuscular disorders, which affect more than 200,000 people in the United States. Most common neuromuscular disesase are muscular dystrophy (MD), myasthenia gravis (MG), and the inflammatory neuromyopathies.

Research advances in laboratory and clinical settings are helping scientists to understand the underlying origins of neuromuscular disorders and to develop more effective treatment. Today 65 percent of the suspected genetic carriers of progressive muscular dystrophy can be identified through diagnostic tests developed by Institute grantees and other researchers. These tests measure the amount of the enzyme, creating phosphokinase (CPK), in the blood serum. Attempts are under way to develop similar tests for identifying carriers in other genetically controlled neuromuscular diseases.

Eight or nine different forms of phosphokinase deficiencies have been identified this year. Phosphokinase is an enzyme in the pathways converting food into related chemical compounds which produce energy for muscle contraction. Through these recent findings and more accurate identification, specific treatments for these disorders are now being formulated. Further studies are in progress to determine the role of this enzyme deficiency at the subcellular level, particularly the conversion of chemical energy into muscular contraction (mechanical work).

Halothane, a relatively new anesthesia favored for surgery with myasthenia gravis patients, was demonstrated even in moderate concentration to produce muscle weakness and relaxation by desensitizing the membrane at the nerve-muscle (neuromuscular junction). The degree of blocking of neuromuscular transmission and the exact site of the action is highly important to the anesthetist with managing patients in whom neuromuscular transmission is impaired.

In another development relating to myasthenia gravis, improvement or complete recovery was found to occur in 89 percent of the female MG patients under 40 years of age when the thymus gland was surgically removed. These facts were obtained in an Institute-supported survey this year evaluating 1,355 MG patients.

In recent months, important diagnostic leads for physicians have developed from findings concerning the effect of remote cancer as a cause of late-onset neuromyopathy. Dermatomyositis, still another of the disabling neuromuscular diseases is the subject of special investigation to determine the actual sensitivity and to find a substance to modify the severe muscle stiffening characteristic of this disease. The family of periodic paralyses are now accurately classified and remarkably well controlled.

Parkinson's disease

Parkinson's disease is a disorder of the brain and nervous system causing rigidity of muscles, uncontrollable trembling of the extremities, stooped posture, lethargy, loss of facial expression, and difficulty in walking, talking, writing, or any action requiring a high degree of muscular coordination. It is estimated to afflict more than 500,000 people in the United States, with 25,000 to 43,000 new cases developing each year. The cause and cure are unknown. Treatment to relieve the symptoms consists of drug therapy and of surgical intervention in a small percentage of cases.

Scientists in many universities and other centers are working to expand the horizons of neurophysiology, biochemistry, epidemiology, and other disciplines bearing on the problem. This year, evidence implicating familial and constitutional factors as causes of Parkinson's disease has been produced in a study of vital statistics records from England and Wales spanning the period from 1855 to 1962. (These records were chosen because they use the most consistent terminology, contain the most extensive data, and cover a longer period than any others in the world.) The study shows a small increase of paralysis agitans in ages 65 to 74 and a more striking increase in individuals dying after the age of 75. There are also indications of a small increase of paralysis agitans mortality during the

period 1926 to 1940—the period during which the Parkinson's sequelae of von Economo's encephalitis reached their greatest prominence.

A critical review of all drugs that have been used in Parkinsonism was prepared, and will be published in 1967. One of the most serious problems in drug therapy for this disorder is the narrowness of the margin between effectiveness and toxicity. Some of the most commonly used anti-Parkinsonism drugs are useful in controlling tremor, for example, only when given in quantities that produce side effects. The review brings together information helpful to physicians seeking to determine the most satisfactory dosage rates for their patients.

Also pointed out are some of the relationships in molecular structure appearing among the synthetic drugs which have been developed in the past 10 years. Many of these drugs have common features in the architecture of their molecules. If these features can be related to specific effects in the body, the synthesis of more effective drugs will be made possible.

Stroke

The brain, because of its high energy requirement, demands over one-fifth of all the blood pumped from the heart. If circulation to the brain fails due to disease of the blood vessels, a stroke results. Stroke is the third largest cause of death in the United States, being responsible for about 200,000 deaths each year.

Much more needs to be known about the various types of blood vessel diseases leading to stroke before preventive or curative measures can be taken. Toward this end, studies involving large populations can be highly useful.

Phase I of the largest and most detailed cooperative statistical study ever conducted on intracranial aneurysms and subarachnoid hemorrhage, one of the major types of cerebrovascular disease, was completed this year. The results, which were collected and analyzed at the University of Iowa, are forming the basis for Phase II, which will ultimately provide physicians with accurate guidance in deciding upon courses of treatment.

Organized 7 years ago among 23 university medical centers, the study has entailed the accumulation of uniform data on 6,368 cases, and a computer-aided analysis of the data. Published results have appeared in eight successive issues of the Journal of Neurosurgery, and have included data on the most common causes of subarachnoid hemorrhage, susceptibility of various age groups, sex distribution, most common sites of aneurysms, sites related to age and sex, percentages of patients who had warning signs, the relation of environmental events to hemorrhage, and the value of angiography in diagnosis. Also produced were new analyses of the mortality of medically (non-surgical) treated cases, the risks of death and of rebleeding at various time intervals after hemorrhage, the statistically critical size of aneurysms, and the influence of age, sex, aneurysm site, and general patient condition on survival.

The scientists found that intracranial aneurysm is the most common cause of subarachnoid hemorrhage (51 percent). Next most common is hypertensive arteriosclerotic cerebral vascular disease (15 percent). Other findings were that the peak frequency for hemorrhage due to aneurysm lies within the 50–54 age group, and that, generally, hemorrhage from aneurysm is more common in women by a ratio of 3 to 2, though men predominate below age 40.

The study showed that headache and dizziness occur before hemorrhage in at least 90 percent of the cases, but noted that these symptoms are so commonplace as to be of little diagnostic value. In one third of the cases, hemorrhage occurred during sleep; in another third, during random activity. However, certain specified events showed a higher frequency of association than expected, including lifting, bending, and emotional stress. The scientists found that high quality, bilateral carotid angiography can be used to diagnose 92 percent of multiple aneurysm cases, but that the remaining 8 percent require vertebral angiography in addition. The study also showed that hypothermia (body cooling) and/or hypotensive treatment (administration of blood pressure-lowering drugs) were not effective in the treatment of bleeding aneurysms, particularly in critically ill patients.

The results of the entire analysis, including newly developed data-handling techniques, have made possible a carefully controlled randomized study, now in progress, in which the various forms of conventional therapy will be compared and evaluated.

Hearing disorders

Hearing is accomplished by an intricate system within the ear which receives sounds, converts them to nervous impulses, which are then transmitted along

nerve pathways to the hearing centers of the brain for interpretation. When sound waves are not conducted properly to the ear structures, or if sound waves do reach the auditory nerve but are not properly converted into a message that can be passed on to the brain, then hearing impairments result.

Estimates of the number of children and adults in the United States afflicted with hearing impairments range upward from a conservative three million, of which an estimated 125,000 are totally deaf. Institute-supported scientists are learning more about causes, prevention, and treatment of impaired hearing.

The effective treatment of certain types of deafness may eventually develop from a new method of directly stimulating the hearing nerve. In the study reported by Institute grantees, the auditory nerve of a 60-year-old man suffering bilateral sensory-neural hearing loss was subjected to direct electrical stimulation over an extended period of time. Six microelectrodes were permanently implanted directly in the auditory nerve, each tiny electrode or combination producing a characteristic pitch. The subject found that he could recognize gross differences between speech sounds when electrical stimuli were presented through the electrodes.

This investigation, designed primarily to evaluate two aspects of perception: (1) the resolution obtainable by discrete stimulation of several small populations of auditory nerve fibers; and (2) differences between precisely controlled electrical stimuli and the more indirect or induction coil-activated stimuli used by many investigators in the past, has been highly important in clarifying many previously controversial problems. This is an example of a promising new approach, which though now in its infancy demonstrates the effort being taken by a number of scientists to develop an artificial ear.

Sodium fluoride is showing favorable laboratory results in treating otosclerosis, one of the major causes of deafness. Minute amounts of sodium fluoride, a chemical commercially used to guard against tooth cavity, has been demonstrated to have the ability to increase calcification of bones and definitely retard the overgrowth of spongy tissue in the cochlea. This technique is used for the treatment of cochlear type of otosclerosis deafness and is not a substitute for the surgical techniques recently developed for the freeing of the stapes.

Women have been found to have a protective difference in ear muscles which may make them better able than men to tolerate noise in certain jobs in industry without suffering permanent hearing loss. This difference also makes it possible for women to tolerate irregular sounds more readily than do men, and to hear higher tones above such noises more easily. These findings have developed this year from the extensive program conducted into the association between noise and hearing loss as an occupational problem in industry.

Rubella infection, found to cause a considerable number of babies to be born deaf, has also been shown to predispose a still larger segment of the infant population to secondary middle ear infection endangering further hearing loss. Detailed records of thousands of mothers and offspring participating in the Collaborative Perinatal Project, are providing figures as to the magnitude of the problem and material for extensive study of the effect of maternal rubella on the hearing mechanism of the child. When the association is known, prompt recognition and treatment of ear infection can often be accomplished thus preventing much of the progressive hearing loss occurring in infancy. Also as part of the Institute's broad attack on the problems of impairment of hearing and speech mechanisms in the very young, a basic test is being conducted at the age of 4 months and an extensive examination at 3 years. Early recognition of any defect of the hearing or speech mechanism is crucial to the learning process and the sociodevelopment of the individual.

A revised concept of bone conduction of sound waves to the inner ear, based on 5 years of experimental work, promises to enable physicians to interpret more clearly the variations in bone conduction measurements found in ear diseases. The main points of the theory involve the three kinds of waves elicited by sound and the three modes of bone conduction responses to the ear. These findings have been integrated with prior knowledge of bone conduction.

The author noted that the response of the normal ear to sound integrates all three modes and the various modifying components according to their amplitude and phase relationships. He emphasized that, when specific parts of the ear are missing or functionally eliminated, the total bone conduction response is altered accordingly.

This is an example of an extensive basic science investigation highly important to the broad problem.

Eye disorders

How one sees has occupied man's concern from time immemorial and, of all the senses, vision has been the most thoroughly studied. The eye is literally an end organ of the brain where the locale of "seeing" actually takes place. The eyeball provides the function of focusing light on the photosensitive retina converting this stimulus chemically into a nervous electrical signal which relays the information to the brain.

Today there are an estimated 411,000 legally blind persons in the U.S.A. and another 3,500,000 partially-sighted. With presently available information, this incidence of visual disability and blindness can be reduced by early detection and treatment. However, the acquisition of fundamental knowledge in understanding the causes and mechanisms which underlie the development of blinding diseases is essential to any major reduction in blindness and visual impairment.

This past year, important research gains have been made which will aid in reducing the number of those with visual disorders.

A major advance in successful corneal grafting and thus the prevention of blindness was achieved recently with a new technique which materially reduces the likelihood of corneal graft failure due to cloudiness. (Corneal grafting is a surgical procedure used to transfer the clear cornea from a donor eye to the eye of a blind person to replace the cloudy portion which is removed.) The new technique involves the interposition between the grafted cornea and the recipient's eye of an inert barrier consisting of a thin transparent sheet of silicone rubber. This barrier is sutured into place along the posterior surface of the graft. It prevents the sensitive posterior membrane (endothelium) of the new cornea from coming in contact with the eye fluids which might react with it.

A few years ago, when surgeons began to use corneal grafts, an unfortunate number of recipient eyes reacted unfavorably to this foreign material. An immunological reaction, inflamation, and swelling with fluid occurred, and new corneas too often became cloudy and opaque, rendering the patients once again blind.

A number of important achievements preceded this newest technique, all of which have helped to alleviate such disasters. A first step was a program to insure maximum viability of the donor material. Then new staining methods, reported last year, were successful in indicating vitality of the donor material. In addition, it was discovered that special freezing methods could preserve donor material until needed by the appropriate recipient.

Recent findings of Institute grantees indicate that many children born with cataracts will have the best chance to see normally if surgery is performed between the ages of 6 and 18 months. If congenital cataracts are removed in late childhood, functional results are likely to be poor, these investigators found. On the other hand, the sooner the surgery, the less likely the development of irreversible changes in the eyes.

Over a period of 5 years the case for early surgery was demonstrated in studies of the visual pathways of developing kittens with cataract or artifically induced blindness. These studies demonstrated that if vision is not permitted during the early months of life, the visual pathways do not develop fully. Even though vision is later restored, the essential functional connections may never be established, and there is permanent visual impairment. A similar situation exists if a muscle imbalance occurs which prevents the two eyes from pointing at the same object. If such a squint is permitted to persist too long, the mechanism for the coordination of eye movements is severely retarded, and there is deep-rooted impairment of the ability to develop binocular vision.

Considerable change in the prognosis and management of certain ocular tumors has been accomplished through the analysis of long-term follow-up investigations of patients. The relatively benign character of certain tumors of the uvea, conjunctiva, eyelid, orbit, and lacrimal gland has become widely appreciated, and efforts are being made to develop more conservative techniques in their treatment. Other tumors are being recognized as highly malignant cancers requiring early radical surgery if the patient's life is to be saved. The more enlightened management of ocular neoplasms, based on better knowledge of their biological behavior, constitutes one of the major advances that have been made in clinical ophthalmology.

Refinements in diagnosis of intraocular tumors, which too often lead to serious visual loss and may create life-endangering situations, have been achieved through long-term studies by Institute scientists and grantees.

As examples, characteristics of malignant tumors of the choroid may now be identified preoperatively by the use of new ultrasonic techniques and instrumentation. In a system developed in the ultrasonic laboratory, an ultrasonic record is produced which has the appearance of an active photograph of the diseased tissue or tumor in the eye. This facilitates recognition of characteristics of different tissues.

Radiation therapy has been reported 84 percent successful in one experimental project in initial and secondary treatment of patients with retinoblastoma (tumor of the retina). This was the first time that supervoltage irradiation has been used exclusively in a uniform manner. The project was reported after patients had been observed for a period of 6 years with no deaths and with generally useful vision.

Lid retraction is both a medical and cosmetic problem, and often results in conjunctivitis and keratitis, due to exposure and dehydration. Prolonged, untreated retraction may eventually lead to corneal ulceration and permanent scarring. Recently 10 percent guanethidine therapy was found to reverse endocrine lid retraction and to lessen the problems of corneal exposure and facial appearance. While further investigation of the possible long-term ocular and systemic side effects of this drug is necessary, it appears possible that the drug may offer a medical solution to this very troublesome problem.

A new synthetic steroid called medrysone has been successfully used with glaucoma patients and normal controls. This drug has anti-inflammatory activity yet is free from the intraocular pressure-increasing affects which characterize certain other drugs used to control glaucoma. It should be a valuable investigative tool as well as a beneficial therapeutic agent.

Because a number of drugs being used in the treatment of systemic disease may have dangerous side effects on the eye, it is important that these side effects be recognized at the earliest moment in order that blindness may be prevented. For example, chloroquine, used to treat arthritis and lupus erythematosus, produces eye damage if given in large doses over prolonged periods of time. The most serious, and irreparable damage is that which occurs to the sensitive neural film—the retina of the eye. A simple test has now been devised to recognize this dangerous reaction in its earliest stages.

ALLERGY AND INFECTIOUS DISEASES

The Institute directs a major research attack against viruses, one of the most important group of micro-organisms involved in infectious diseases and the cause of an estimated 60 percent of all episodes of human illness.

VACCINE DEVELOPMENT

A broad goal of the highest priority is the development of effective methods for preventing viral respiratory disease, the most common infectious ailment of man. Prospects for achieving this goal through collaborative efforts to produce and test protective vaccines continued to be bright. The vaccine development program, based on a close partnership of industry, universities, and Government, carried on concerted efforts to develop vaccines against adenoviruses, parainfluenza viruses. *Mycoplasma pneumoniac*, respiratory syncytial, rhinoviruses, and rubella.

The major accomplishment of the program has been the production of an effective live oral vaccine against adenovirus type 4 infection, a particularly serious health problem among recruits in military training camps. The vaccine capsule does not break up and release virus until it reaches the intestines, where it causes a symptom-free infection that stimulates the production of antibodies. Extensive trials, involving 50,000 recruits, were conducted at For Dix, New Jersey; Great Lakes Naval Training Center, Illinois; Parris Island, South Carolina; and Camp Lejeune, North Carolina. Additional studies of selected populations have been conducted at the University of Illinois, Lorton Reformatory, the University of Colorado, Fort Ord (California), and in the Netherlands. Analysis of the data was nearing completion at the end of the year. The success of the adenovirus-4 vaccine is indicated by the desire of the armed services to administer it to half a million military recruits during the next year.

There was also progress in a modest but highly promising program of research on soluble antigens of adenoviruses. In previous tests, soluble antigens produced significant antibody concentrations against adenoviruses 1 and 2. This

work was followed up in the past year when similar results were achieved with adenovirus 4. Adenoviruses 1 and 2, along with adenoviruses 4 and 6, make up one of the three major antibody-producing groups into which, Institute scientists reported a year ago, the adenoviruses fall. The results suggest the possibility of a polyvalent soluble-antigen vaccine against several adenoviruses. This is important because some adenoviruses cause tumors in hamsters and cannot be given as a live vaccine.

An advance was made toward the goal of an effective vaccine against the parainfluenza viruses, important causes of croup, bronchitis, and pneumonia in infants and young children. A prototype vaccine against the three types of parainfluenza viruses proved effective in field trials at the University of Colorado; Fort Ord; the Children's Hospital of the District of Columbia; and Junior Village, a District of Columbia institution. More extensive trials are planned.

Last year, a novel method of growing *M. pneumoniae* in mass culture was developed: The organism was adapted to growth on a glass surface. Organisms grown in this manner can be washed a number of times without becoming detached from the glass. This makes it possible to prepare highly concentrated suspensions of organisms. This past year, the method of growing *M. pneumoniae* was applied to the preparation of a simpler, cheaper, highly purified prototype inactivated vaccine which has 10 to 100 times to potency of previous experimental vaccines. An advantage of the more concentrated vaccine is that it can easily be added to other vaccines. The new vaccine showed promise in tests at the University of Maryland, Camp Lejeune, and Keesler Air Force Base (Mississippi). It will be further tested in larger populations.

Many obstacles still stand in the way of a vaccine against respiratory syncytial virus. This virus produces its major impact during the first six months of life and causes about half of the 10,000 infant deaths from pneumonia each year in the United States. But some progress was made. At the end of 1966, a vaccine preparation was being tested in several populations. In addition, two different antigens of respiratory syncytial virus had been characterized and a system for testing vaccines had been developed.

The goal of an effective vaccine against the common cold is difficult to achieve because of the multitude of different viruses, particularly the numerous rhinoviruses, which are involved. However, it may be possible to select and group the rhinoviruses that are chiefly implicated. A major step in this direction was taken when the rhinovirus typing center, a contract facility of the vaccine development program at Children's Hospital of Columbus, Ohio, completed typing about 100 rhinovirus strains. This work was presented to the International Congress for Microbilology at Moscow in July 1966 as the basis of an internationally accepted classification for all rhinoviruses. It will now be possible to study the antigenic relationships among the rhinoviruses. Knowledge of these may lead to prototype rhinovirus vaccines.

The newest vaccine program is aimed at the development of live attenuated and killed vaccines against the rubella virus. This virus (German measles) causes severe congenital defects in babies whose mothers are infected in early pregnancy. Progress has been rapid. Plans have already been made to test vaccine preparations in selected population groups. Additional vaccine-evaluation centers have been established to evaluate potential rubella vaccines. Considerable experience and training have been gained in cultivating and testing rubella virus. And methods were developed for economically producing complement fixing antigens to be used in determining rubella immunity.

VIRAL RESPIRATORY INFECTIONS

The development of effective vaccines against diseases of the respiratory tract depends in good part on continuing efforts to broaden understanding of the relationships between virus infections and diseases.

Extensive studies brought new light on the roles of breathing, speaking, coughing, and sneezing in spreading respiratory disease. Coughing was shown to be the most important source of airborne viral particles, and human-to-human transmission via the airborne route was conclusively demonstrated. Airborne influence virus was found to be highly infectious. Very low doses of virus administered by aerosol inoculation produced influence in volunteers. Thus, small amounts of virus may be sufficient to transmit the disease.

A 4-year extensive study of virus infections in two large contrasting communities in the New York metropolitan area yielded valuable epidemiologic data on

viral respiratory disease by attempting to determine how frequently respiratory infection results in disease. Preliminary results showed that rhinoviruses were the leading cause of acute respiratory illness, followed by the parainfluenza viruses. The adenoviruses and enteroviruses (polio, Coxsackie, and echo viruses) were also—but less—involved in respiratory illness. Another 4-year epidemiologic study also showed the importance of the rhinoviruses in causing common cold-related illnesses in young adults. Rhinoviruses made up 80 percent of the agents isolated in the latter study, which focused on upper respiratory infections occurring among medical students at the University of Chicago. Still another long-term epidemiologic study—at the Parris Island, South Carolina, Marine recruit training center—provided the first evidence that reinfection with *M. pneumoniae* occurs under natural conditions.

VIRUSES AND CANCER

It is becoming increasingly clear that a number of viruses, including several that occur in humans and other primates, are capable of causing tumors in a variety of laboratory animals under experimental conditions. New discoveries in the behavior of these and other oncogenic viruses provided exciting new approaches to the study of human cancer.

Institute scientists have been at the forefront in work leading to one of the most significant advances in virology in many years—the discovery of the T antigens, which are found in virus-induced tumor cells in which no virus can be demonstrated. Studies in molecular biology and in serology (the study of antigen-antibody reactions) provided additional evidence that the T antigens present in adenovirus tumors are determinants of oncogenesis. As a result of these findings, the director of the National Cancer Institute called together an *ad hoc* committee, which included Institute scientists and grantees, to survey human cancer patients for evidence of antibodies to the antigens of adenoviruses and other viruses.

It was found that Bryan Rous sarcoma and Moloney sarcoma viruses are defective (that is, their sets of genetic materials are incomplete) and depend on a mouse leukemia "helper" virus to produce a complete infectious virus. These and other related findings suggest a new approach in the search for the cause of human and animal sarcomas and leukemias.

It was convincingly demonstrated that viral genetic material is present in adenovirus–12 tumor and transformed cells. A very small amount of adenovirus–12 deoxyribonucleic acid (DNA), the chemical that transmits genetic information, was found to produce large amounts of messenger ribonucleic acid (mRNA), another chemical that carries the information from the DNA to the cellular particles where the information directs the production of protein. This finding provided evidence that the adenovirus-induced mRNA stimulated the particles to produce abnormal proteins responsible for starting the cancer process and continuing it—even in the absence of detectable virus.

The sensitivity of cells from adenovirus-induced tumors to calcium was found to provide a useful test for determining whether a tumor was induced or a tissue culture cell line transformed to the cancerous state by adenovirus. Calcium sensitivity may be a valuable aid in studying the role of adenoviruses in causing tumors because (1) certain tumors arising after an inoculation with adenovirus may not have been caused by this virus, and (2) certain cell lines derived from adenovirus-induced tumors contain insufficient tumor antigen to be detected by directly testing the cells for antigen content.

"SLOW VIRUSES"

Research continued on another area of virology, that of the chronic progressive virus infections, in which a long time elapses between the initial virus infection and clinical signs of disease. Several "slow virus" diseases of animals are being studied because they may bear an important relationship to chronic degenerative diseases of man, such as multiple sclerosis. Four of these diseases that may have biologic counterparts in man are scrapie, (a disease that naturally affects sheep and, less frequently, goats) encephalopathy of mink, Aleutian disease of mink, and chronic interstitial pneumonitis of sheep.

Scrapie was studied in goats. In these animals, the disease is characterized by a prolonged latent period, during which virus can be detected, and by the subsequent growth and dissemination of virus in lymphocytic tissue before the

central nervous system (CNS) is invaded. Preliminary observations indicated that encephalopathy of mink has a similar development.

A brain disease has attacked mink on nine Wisconsin mink farms during the past 15 years. The disease was studied and found to have a long incubation period similar to that of scrapie.

Aleutian disease of mink is characterized by an entirely different type of virus growth from that of scrapie. Virus appears quickly and persists until the animal dies. Preliminary findings, indicated that chronic interstitial pneumonitis of sheep, which was reproduced experimentally and shown to be caused by a slow-growing filterable agent, develops in a similar way.

MEASLES

In this country, death from uncomplicated measles is rare. However, particularly in infants, measles may be followed by bronchopneumonia and other bacterial infections, which may be fatal. Hence, the importance of a mass vaccination program to wipe out measles. Furthermore, reported cases of measles encephalitis have increased from 96 in 1965 to 157 in the first 40 weeks of 1966. New evidence was found to strengthen indications that the measles virus directly attacks the CNS. Also, a series of experiments indicated that apparently measles can adversely affect the reading-readiness scores of children. In addition, a rapid, reliable test was found effective in the differential diagnosis of the disease, which frequently must be distinguished from other illnesses that are responsible for measles-like rashes. This inexpensive test uses the immunofluorescent technique to demonstrate the presence of measles-virus antigen in the epithelial cells of human urinary sediments.

HERPES VIRUSES

Another agent implicated in disease of the central nervous system is the herpes simplex virus, which causes the common cold sore or fever blister. In one Institute-sponsored study reported in 1966, 18 of 52 patients with herpes simplex infections were found to have encephalitis or meningitis as a result of the virus. Herpes simplex must sometimes be differentiated from other illnesses, such as herpes zoster (shingles) and varicella (chickenpox). Work advanced on a more efficient method for early diagnosis of herpes simplex infections, based on the detection of complement-requiring neutralizing antibody to herpes simplex virus in the sera of infected patients. An animal model system was devised for the study of recurrent herpes infections. With this system, herpes lesions occur in latently infected rabbits 1 to 5 days after the animals are inoculated with epinephrine. Another development was an immunofluorescent test that rapidly identifies isolates of the varicella-zoster virus, which causes both shingles and chickenpox. This may lead the way to improved laboratory diagnosis of these infections.

REOVIRUSES

Reoviruses received increased attention because (1) they have been implicated in acute respiratory disease, rashes, and hepato-encephalitis, (2) their prolonged growth cycle and tendency to accumulate within the cell possibly involves them in chronic virus infections, and (3) their structure may give them a tumor-producing potential. Grant-supported investigators of this Institute and of the National Cancer Institute established an animal model to study reovirus infections. They found that congenital reovirus infections, not previously described in animals or man, were produced by inoculating pregnant mice with reovirus type 2.

TESTS AND TECHNIQUES

A fast, simple test for diagnosing infectious mononucleosis, a disease presumed to be caused by a virus, proved to be a practical clinical tool. The serum of patients with this disease contains antibodies capable of agglutinating the red cells of other species, particularly sheep. A high concentration of these antibodies establishes the diagnosis. It was found that the agglutination of red cells is enhanced when they are made to descend through an antibody solution in a capillary tube.

Another accomplishment was a color test for measuring antibody to T-strain mycoplasmas, which may be implicated in nongonococcal urethritis and other diseases whose causes are obscure. The test is based upon the ability of T-strain

mycoplasmas to metabolize urea, thereby producing ammonia, and the ability of specific antisera to inhibit the production of ammonia. The results demonstrate the feasibility of a serological approach to the study of the T-strain mycoplasmas.

Another useful tool—the "cell pack" procedure—was developed to provide "diagnostic antigens" for numerous viruses that cause or are suspected of causing, human illness. In this method, various high-titered complement-fixing antigens are concentrated in cell cultures by slow-speed sedimentation of undisrupted virus-infected cells and removal of the supernatant medium. The technique is reliable and economical and has the value of simplicity.

SMALLPOX

Significant advances were made in the control and treatment of smallpox. An attenuated live smallpox vaccine was developed and brought to the stage of clinical evaluation. It promises to be valuable in immunizing children and adults who have eczema, a condition in which standard vaccination may lead to eczema vaccinatum, a potentially fatal complication. It was found that clotting abnormalities occur before serve bleeding in hemorrhagic smallpox. As a result, treatment of this serious condition with an anticoagulant such as heparin will be attempted.

ANTIVIRAL SUBSTANCES

In 1963, prophylactic treatment of smallpox with the antiviral drug N-methylisatin-b-thiosemicarbazone was the first successful attempt at chemoprophylaxis of a major virus disease affecting man. This work moved forward. Tests continued to show that the drug is effective in protecting people exposed to smallpox, even those who have never been vaccinated. The drug was also found to work against alastrim, or variola minor, a less severe form of smallpox.

Studies continued on the antiviral effects of the amantadine compounds. These drugs have shown strong evidence of an inhibitory effect on myxoviruses (a group that includes the influenza, parainfluenza, and mumps viruses). Another compound, RO5-3369, also showed some activity against these viruses.

Investigators carried on laboratory studies of the antiviral effects of various plant extracts. Crude extracts of mushrooms showed an inhibitory effect on influenza. Extracts of the lemon balm plant, used medicinally since antiquity, continued to show promise against herpes simplex and vaccinia viruses.

Methotrexate, an anticancer drug, was found to greatly improve the vision of patients with sympathetic uveitis. The drug was found to be an improvement over previous treatments, since the vision of some patients was restored.

The gradient plate technique, of great usefulness in investigating antibiotic activity, was adapted to the study of virus inhibition by known antiviral compounds, including the pyrimidine nucleosides, the thiosemicarbazones, amantadine, guanidine, and -hydroxybenzylbenzimidazole—all of which, when tested with the technique, produced antiviral effects. The technique was also found applicable to the bioassay of 5-iodo-2′-deoxyuridine (IUDR), which is effective against herpes simplex and vaccinia viruses, and to the detection and isolation of IUDR-resistant strains of herpes simplex virus.

New light was cast on the antiviral role of interferon, a substance produced by living animal and human cells in response to virus infections. A team of Institute scientists, building on earlier findings by other investigators, assigned a message-transmitting function to interferon. According to the new theory, interferon does not itself act directly against a virus. Instead, interferon "transmits a message" to cells and stimulates them into producing another material that is the actual antiviral substance.

Investigations continued on a number of substances shown to be capable of inducing interferon-like inhibitors. These include bacterial endotoxins, nucleic acids of viral and nonviral origin, and statolon and helenine—both derived from *Penicillium* molds. The results of extensive research on helenine added further evidence that this antibiotic-like substance exerts an antiviral effect by inducing the formation of interferon.

VIRUS REAGENTS

Research on interferon will be advanced by supplies of this antiviral substance to be made available by another collaborative program of the Institute, that responsible for the production of virus and other research reagents. Production and testing of crude mouse interferon and partially purified chick interferon were provided by contract. The chick interferon reached the final stages of production.

The number of virus reference reagents—ampoules of carefully tested virus suspensions and corresponding antisera—distributed reached more than 25,000. These identity tags were distributed to qualified investigators all over the world to enable them to identify a wide range of viruses.

OTHER RESEARCH ON VIRUS DISEASES

Institute scientists of the Middle America Research Unit, Canal Zone, found evidence that Machupovirus, which causes Bolivian hemorrhagic fever, and related viruses may be transmitted to man from chronically infected rodents that excrete large quantities of the virus in the urine for many months.

Other Institute investigators reported the first known cases of humans infected by hamster-transmitted lymphocytic choriomeningitis, an influenza-like illness.

Institute grantee-contractors added to the comprehensive data they have published on the 1964 epidemic of St. Louis encephalitis (SLE) in Houston, Texas. They found that, in the summer during the epidemic, a significant number of enteroviral infections and several dual SLE-enteroviral infections were observed. These and SLE infections could not be clinically differentiated. During the summer, all three must be considered in the diagnosis of acute febrile CNS disease.

ALLERGY-IMMUNOLOGY

Intensive studies of the immune response (that is, of how and why the body makes or fails to make antibodies in response to an antigenic stimulus) underlie the Institute's work in allergy and immunology. A greater understanding of the immune response is basic to progress in efforts to master the complex problems of organ and tissue transplantation, autoimmune disorders (in which the body reacts to its own tissue antigens), and allergic diseases.

Transplantation and the immune response

The critical problem in transplantation is to find methods of controlling the immune response so that people receiving transplanted organs will not reject them. In another of the Institute's collaborative programs—the transplantation immunology program—intensive efforts continued to be directed toward the solution of this problem.

If the transplantation of tissues and organs between one human being and another is to become an effective procedure, the donor of the graft must be chosen so that he has as many antigens as possible in common with—and as few as possible which are absent in—the recipient. The procedure of donor-recipient matching can be summed up in two words—"tissue typing." Nine collaborating laboratories in the United States and Europe carried on their efforts to develop standardized techniques for tissue typing.

Groups of leukocytes (white blood cells) used as reference antigens were being characterized by various techniques so that a battery of these standardized antigens may be established. And antisera (blood components which have antibodies) were being collected. Over 40 liters of well-characterized typing material were collected and were being made available to investigators for further studies in donor-recipient matching.

Surgeons continued to collaborate with several investigators in the transplantation immunology program in a prospective and retrospective study of tissue typing in kidney transplantation. Several groups have added to the evidence that there is a high correlation between the compatibility of leukocytes in the donor and recipient and the success of kidney transplantation in humans. Another important finding was that membranes isolated from group A hemolytic streptococci can induce strong hypersensitivity to skin homografts in the guinea pig. This has led to the hope that stable antigens from this source can be produced and substituted for the costly and difficult-to-produce leukocyte antigens in tissue typing and that eventually they will make recipients tolerant to foreign grafts. Human fibroblasts growing in culture are also being used as a source of antigens.

The Institute also supported other basic and clinical research in transplantation immunology and related work at medical institutions throughout the Nation.

Observations by a group at one of these institutions established that subcellular fractions can induce homograft sensitivity. Pretreatment of the prospective adult recipient with these fractions can produce prolongation or acceptance of the transplant when the antagonism between tissues is weak. This approach holds the promise of producing adult tolerance (lack of response to an antigen),

antigen overloading (in which a large amount of antigen induces immunologic paralysis), or desensitization in the prospective recipient to enable him to retain the transplant.

A research team reported the results of efforts to prolong graft survival by heterologous antiserum to lymphocytes—in which antiserum derived from an individual of a different species depresses the action of antibody-producing cells sufficiently to interfere with homograft rejection. Renal transplants in dogs treated with an antiserum produced in a horse immunized with dog lymphocytes survived for long periods—two, beyond 350 days. The results of work by this group suggest that a brief period of intense treatment with antiserum to lymphocytes may increase the effectiveness of chemotherapeutic agents and steroids and decrease the doses required to maintain suppression of the immune response. Experiments conducted by the team also indicated that heterologous antiserm to lymphocytes may be useful in producing specific tolerance in large animals.

Another team, the one that in 1954 performed the first successful kidney transplantation between humans, found that the effect of thoracic duct cannulation (in which lymphocytes are drawn off) on the immune response shows promise as a supplementary method of suppressing the homograft rejection response. When large numbers of lymphocytes were cumulatively drawn off, patients had smoother post-transplant courses; rejection appeared to occur less frequently and to be more easily treated in the patient with a well-draining thoracic duct.

A university group worked on a rather promising approach to selecting compatible donors for human organ transplantation: If mixtures of viable lymphoid cells from two genetically unlike members of the same species (for example, mice) are injected into the skin of a heavily irradiated hamster, delayed cutaneous inflammatory reactions develop at the sites. The intensities of these reactions are related to the extent of the antigenic differences between the two donor animals. Preliminary studies in man, using lymphocytes obtained by fractionation of peripheral blood, gave evidence of the test's usefulness for donor selection. A similar result was obtained in experiments conducted by Institute scientists.

In other extramural research, it was reported that (1) antiserum to thymus, a gland that plays an important role in antibody production, results in more persistent reduction of lymphocytes and prolongs the survival of transplanted grafts more markedly than antiserum to lymphocytes, and (2) large numbers of renal tubular cells in the urine of a patient who has received a kidney transplant may signal the threatened rejection of the graft.

The Institute also conducted at its own laboratories in Bethesda, Maryland, basic immunologic studies related to graft rejection.

At least 14 loci (sites of the genes that control the production of tissue antigens) are involved in the acceptance or rejection of grafts in mice. One of these, the H–2 locus, is the most important. Institute scientists found that pretreatment of donor mice with any of a wide variety of antigens greatly diminishes the ability of their lymphoid cells to evoke in recipient mice graft-versus-host reactions across H–2 histocompatibility barriers. The reason is apparently the reduced ability of the donor cells to respond to a second unrelated antigenic stimulus. This kind of modification of donor immunocompetence represents a novel approach to the development of transplantation tolerance in higher mammals.

Immunologic research in kidney disease

Over 75 percent of kidney failure results from two forms of nephritis, or inflammation of the kidney: (1) glomerulonephritis, originating in the glomeruli that filter the blood into the kidney tubules, and (2) pyelonephritis, originating in the pelvis of the kidney. These disorders were the focus of intensive research. Their control or elimination would go far toward decreasing the need for kidney transplantations and for artificial kidneys.

One group of grant-supported investigators carried on a long-term study of the mechanisms by which immunologic events may injure glomeruli. Two mechanisms were revealed, both dependent upon serum antibody, with no evidence of direct injury by sensitized cells: (1) circulating antibodies react with antigens fixed in the glomeruli, and (2) circulating antigen-antibody complexes immunologically unrelated to the kidney localize in the glomeruli. Once the immunologic reactants are in the glomeruli, there is probably a single effector mechanism by which these two mechanisms cause glomerular injury. In another long-term immunologic study, a number of human, clinical forms of glomerulonephritis were related to the two foregoing mechanisms.

The kidney disorders caused by antiglomerular antibodies include experimental allergic glomerulonephritis, which is induced by immunization with glomerular tissue. The disease was transferred with serum antibody from nephritic donors to normal recipients. This work, done in sheep, was the first clear-cut demonstration of transfer by serum of one of the auto-immune diseases. A similar but less consistent serum transfer of experimental allergic glomerulonephritis was achieved in rabbits.

Acute pyelonephritis is usually caused by gram-negative enteric bacteria. Although bacteria and mycoplasma have been suggested, it is not certain what causes the chronic form of the disease. By subjecting germfree and conventional rats to urethral ligation (thus preventing them from excreting organisms). Institute scientists confirmed that chronic pyelonephritis can be produced in animals in the absence of bacteria and mycoplasma; therefore, infection may not be essential for the disease.

Allergic diseases

A highlight of research in allergy was the development of a blood test for reactions to ragweed pollen. The test, which is still experimental, measures the histamine released when the white blood cells of allergic people are exposed to ragweed-pollen antigen. The new test, which is 20 times more sensitive than the skin test now used, may also work with antigens other than those of ragweed.

New findings opened the way for a more effective attack on farmer's lung disease, a disorder of hypersensitivity found among agricultural workers. Investigators purified the soluble antigens from both moldy hay and *Thermopolyspora polyspora*, the organism implicated in farmer's lung disease, and showed that these antigens are similar.

Allergic reactions to penicillin have become a serious problem. About 15 percent of the American people are estimated to be sensitive to the antibiotic. Findings in an extensive 6-month study of hospitalized patients treated with penicillin underscored (1) the need for caution in administering penicillin to patients with previous adverse drug reactions or with such allergic conditions as eczema, hay fever, and asthma, and (2) the problems involved in using the penicilloyl-polylysine skin test for penicillin allergy, a promising test that has been the subject of intensive study since 1962, chiefly under Institute support.

BACTERIAL DISEASES

The treatment of bacterial diseases is marked by a continuing battle between antibiotic agents and drug-resistant strains of bacteria.

Pneumococcal infections are a case in point. Tetracycline has proved effective against these infections. But an Institute-supported study revealed that, although still rare, tetracycline-resistant pneumococcal infection has been reported from worldwide sources within the last few years. It appears that resistant strains have developed as a result of the extensive use of tetracycline and are now more prevalent. Epidemiologic data, although limited, suggest that human-to-human transmission of such strains is possible. And a resistant strain was isolated from an asymptomatic patient 4 months after his discharge from the hospital.

Similarly, recent studies showed that the meningococci are becoming increasingly resistant to the sulfa drugs. It was recognized that new approaches to the prophylaxis of meningococcal infections among military recruits and exposed members of the civilian population are required, particularly since these infections were more prevalent in the United States from January to June 1966 than in the same period for 1965. Preliminary work suggested possible treatment with Trimethoprim (trimethoxybenzyl pyrimidine) together with sulfonamides or antibiotics.

Staphylococci

Staphylococcal disease continues to cause serious trouble. The organisms may persist in the tissues for a long time, and in the resulting extended treatment with antibiotics, drug-resistant strains emerge.

The Institute continued to conduct and support biochemical studies of the enzymatic activities associated with the formation and breakdown of staphylococcal organisms. The goal of this work is an understanding of how some antibiotics affect the growth of the organism and how the organism becomes resistant to the drugs. Enzymes that destroy bacteria were investigated as pos-

sible therapeutic agents. One of these—Lysostaphin—showed real potential in the treatment of severe staphylococcal disease. The enzyme Chalaropsis B also showed promise.

Another approach that showed interesting possibilities was that of bacterial interference, in which a harmless staphylococcal strain is colonized in a site—for example, by nasal implantation—to prevent colonization by a virulent strain.

A promising experimental vaccine against *Staphylococcus aureus* was developed from heat-killed whole, washed cells of the organism and tested in mice. The soluble cell fraction that confers immunity in mice was identified.

Streptococci

Important work on a vaccine against another group of disease-causing bacteria—the streptococci—was carried out by grantees of the Institute and the Institute of Arthritis and Metabolic Diseases. The experimental polyvalent vaccine is composed of highly purified M proteins (antigens) extracted from the cell walls of group A hemolytic streptococci. The goal is to include in the vaccine M proteins from each of the important disease-causing streptococcus serotypes. The polyvalent vaccine has been tested in rabbits. M proteins from type 12, as well as type 24 and some type 14, streptococci have been tested in human beings. Type 12 is particularly significant since it is associated with glomerulonephritis resulting from streptococcal infections.

Another group of investigators conducted experiments with a mixture of polypeptides of type 12 streptococci. They found that a component of this mixture, which causes kidney damage in laboratory animals, can be localized and retained in kidney tissues. There were indications that this component is an antigen. The results of these studies may lead the way to an understanding of how streptococcal polypeptides damage the kidney.

Evidence indicates that the group A streptococcus is the probable causative agent of acute rheumatic fever. Search continued for complete proof. One piece of evidence was the finding that a single injection of a sterile extract of group A streptococcal cells induced in the hearts of mice lesions that were similar to the cardiac lesions of rheumatic fever.

Bacterial L-forms (colonies of protoplasts—cellular or subcellular units of bacteria that have been deprived of a rigid cell wall) continued to receive increasing attention. Studies were conducted on the different sensitivities of protoplasts and the parent bacterial form of *Streptococcus faecalis* (a normal inhabitant of the intestinal tract and a cause of bacterial endocarditis). This work led to greater insight into the mode of action of antibiotics and of antibiotic synergism (when two drugs exert a greater combined effect than either one by itself can).

Institute scientists discovered very small elementary bodies in the ultrathin sections of L-forms of group A streptococci. This finding promises to lead the way to an understanding of particular bacterial functions, especially those involved in essential biosyntheses which may be blocked by drugs or altered by genetic mechanisms.

Gram-negative rods

Infections that result from gram-negative rod-shaped bacteria, particularly *Salmonella*, *Shigella*, *Escherichia*, *Aerobacter*, and *Proteus*, continue to be a serious problem. *Salmonella*, *Shigella*, and enteropathogenic *Escherichia coli* are the chief pathogens involved in diarrheal disease, and important cause of infant deaths attributed to infectious diseases.

The resistance of the gram-negative rods to antibiotics—many have multiple-drug-resistant strains—is of great significance to the therapy of infectious diseases. For this reason, efforts directed at improved antibacterial therapy were intensified. The mechanisms invloved in multiple drug resistance were intensively studied. It was found that gram-negative bacteria are developing resistance even against previous drugs of choice, such as kanamycin and neomycin—creating a very serious challenge to the antibiotic arsenal.

Sodium ampicillin, a form of ampicillin recently developed for parenteral administration, was found effective against infections caused by *Escherichia coli*, *Proteus mirabilis*, *Hemophilus influenzae*, *Diplococcus pneumonia*, non-penicillinase-forming staphylococci, and enterococci.

Cephaloridine, a semisynthetic antibiotic, was clinically investigated. It appears to be effective against uncomplicated *E. coli* infections. It may become the drug of choice against *Proteus mirabilis* infections, which are associated with such conditions as pleuritis, peritonitis, and cystitis.

Research continued on bacterial infections of the urinary tract, which are particularly serious in infants and young children. The enterobacteriaceae make up the family of gram-negative rods chiefly involved in these infections. Nalidixic acid, a relatively new orally administered antimicrobial drug, has been the subject of numerous reports attesting to its effectiveness against urinary-tract infections. Institute grant-supported investigators submitted the drug to careful evaluation and found that, although it has effective bacterial action against most enterobacteriaceae, it has a strong tendency to evoke highly resistant strains. Thus, the drug unfortunately has limited usefulness in the treatment of chronic urinary-tract infections.

A clinical study revealed that many failures in antimicrobial treatment of chronic urinary-tract infections probably result from reinfections with new, resistant strains of organisms rather than from relapses with the same organism that was present before therapy. The findings underscore the need for precise identification of enterobacteriaceae to distinguish relapse from reinfection.

Such a work of identification was applied to another group of gram-negative bacteria—the pseudomonads. The most important member of this group is *Pseudomonas aeruginosa*, which results in various infections, including pyelonephritis, and is an important cause of hospital infections in debilitated patients. A detailed analysis of the pseudomonads brought to light many previously unrecognized characterisics of these bacteria and made possible recognition of a number of species which can be readily and clearly distinguished from one another.

Cholera is another disease caused by a gram-negative rod. The Institute assumed new responsibilities in connection with this disease when its scientific director was appointed chairman of the National Institutes of Health Cholera Advisory Committee. This appointment entails the scientific management of (1) the SEATO cholera research program, developed as a result of the spread of cholera in southeast Asia, the Pacific, and westward from its traditional endemic focus beginning in 1958, and (2) the Pakistan-SEATO Cholera Research Laboratory in Dacca, East Pakistan. During the year, the laboratory made notable contributions by (1) providing information on the effectiveness of the U.S.-manufactured cholera vaccine in preventing the disease, (2) determining the long duration of vaccine-induced immunity, particularly in adults in areas where cholera is endemic, (3) acquiring additional data on the value of tetracycline in the therapy of cholera, (4) issuing new information on noncholera diarrheas, and (5) recognizing hypoglycemia as a complication of cholera in infants.

Tuberculosis

Tuberculosis is still a major health problem in the United States, where it takes 10,000 lives and accounts for 50,000 new active cases each year.

An increasing number of patients with pulmonary tuberculosis are found to be infected with mycobacteria resistant to major antituberculosis drugs such as streptomycin, isoniazid, and para-aminosalicylic acid. As a result, there was no letup in the search for effective drugs for re-treating pulmonary tuberculosis. One major finding reported during the year was that kanamycin, when used in combination with other antimycobacterial agents, is effective in re-treating patients infected with drug-resistant tubercle bacilli.

The Institute continued its work on a cell-wall vaccine to prevent experimental tuberculosis. This work went forward with the aid of an active and specific protection test based on pulmonary infection of vaccinated mice. Progress was made in determining factors that influence the immunizing potency of the vaccine, and procedures were established to make its preparation practicable. However, a setback came with untoward reactions that resulted when the vaccine was tested in rhesus monkeys. Attempts were undertaken to isolate and purify the components responsible for provoking the reactions.

Other research

Other noteworthy research accomplishments in bacterial diseases were (1) the highly promising results obtained in clinical studies with the antileprosy drug B.663, a phenzane dye compound and (2) the knowledge gained of the histamine-sensitizing activity and the antigens of various strains of *Bordetella pertussis*—which holds promise of leading to the development of a purified vaccine for immunizing children against whooping cough.

PARASITIC DISEASES

The Institute continued to conduct and support research on the principal parasitic diseases of man, including malaria, schistosomiasis, amebiasis, and toxoplasmosis.

Malaria

Widespread efforts are being directed toward the control and eradication of malaria, which is still one of the major worldwide causes of illness and death. But progress has been held back by the emergence of strains of falciparum malaria (the most severe form of human malaria) resistant to previous synthetic drugs of choice and, in some cases, even to quinine.

Because of the critical importance of drug resistance in human malaria, the Institute continued its studies on the experimental chemotherapy of the disease, with emphasis on the newer drugs, on combinations of drugs, on ways of administering these drugs, and on the mechanisms of action and resistance.

Trials of CI-564 (a combination of cycloguanil pamoate and acetylated diaminodiphenyl sulfone—DDS) against multiresistant strains of falciparum malaria from several areas of southeast Asia were somewhat encouraging; in most cases, CI-564 successfully protected volunteers from, or cleared them of, infection.

During the year, four additional strains of drug-resistant falciparum malaria, all from southeast Asia, were isolated and studied in volunteers. These strains were highly resistant to antimalarials. Two even showed some resistance to normal courses of quinine and required extended therapy with this drug.

The urgent need to provide alternative methods of treating the resistant strains prompted research on the sulfa drugs, either alone or in combination with pyrimethamine. Three of these sulfa drugs,—sulfadiazine, sulfamethoxypyridazine, and sulforthodimethoxine were evaluated in volunteers. These drugs were not reliable when used alone but were effective when used in combination with pyrimethamine. Sulforthodimethoxine, when combined with pyrimethamine, was the most promising for treating resistant falciparum malaria. But there are disadvantages in using the sulfa drugs, even in combination with other drugs: parasites may develop resistance, response to these drugs is relatively slow, and toxic side-effects are likely to develop when long-acting sulfonamides are used.

Forty-nine new compounds were tested orally and by injection in mice against *Plasmodium berghei* (the rodent malarial parasite). The most active of these compounds was 2-sulfamilimide-3-methoxypyrizine. It was highly effective against both the normal and the chloroquine-resistant strains of the parasite. Its activity was equal to sulforthodimethoxine and sulfamethoxypyridazine and superior to DDS or sulfadiazine. These results were confirmed when the compound was tested in monkeys against *P. cynomolgi* (the monkey malarial parasite). The drug shows potential as an alternative to the standard antimalarials against the multiresistant strains of falciparrum malaria.

An effective vaccine against malaria is a possibility. In Institute grant-supported research, mice were immunized against a normally fatal species of rodent malarial parasite. Once established, immunity persisted at a high level for many months.

Schistosomiasis

Schistosomiasis ranks second only to malaria as the parasitic disease that causes the greatest number of illnesses and deaths. In long-term clinical field studies, the search continued for improved ways of using the antimonial drugs against the disease.

One study was carried on in Puerto Rico with the cooperation of the School of Medicine, San Juan, and the Rio Piedras Hospital. Slow continuous infusions or closely spaced injections of stibophen or of Astiban (sodium antimony dimercaptosuccinate) were found to give improved therapeutic activity against *Schistosoma mansoni*, the blood fluke (trematode worm) that infests man, and to be better tolerated than when conventional schedules employing widely spaced injections were used.

The other field study was conducted in Alexandria, Egypt, in cooperation with the High Institute of Public Health, Alexandria, and the University of Alexandria. This 4-year study of the suppressive, therapeutic and prophylactic effects of certain antimonial compounds reached the final or post-treatment phase. Urinary shedding of *S. hematobium* (the fluke, common in Africa, found in vessels of the urinary bladder) ended in about 90 percent of people who received a single

monthly injection of Astiban. Moreover, urinary shedding did not resume in any significant number of these people during a 6-month period after therapy was stopped. The findings indicated that the drug in the regimen used has both protective and therapeutic properties and is suitable for a mass treatment in hyperendemic areas.

Amebiasis

Research on amebiasis also involved evaluation of promising new drugs.

Institute scientists opened the way to more effective laboratory testing of drugs. They developed a clear liquid medium for growing axenic cultures (free from foreign organisms) of *Entamoeba histolytica*, the organism that causes amebic dysentery and abscess of the liver. These cultures made available for the first time a system for testing drugs directly against the organism. In previous culture systems, tests were inconclusive because it was hard to rule out the effects of a drug on microbes serving as food for the amebae. Axenic cultures of amebae will also greatly help in the study of nutritional requirements of *E. histolytica*, its physiology, the mechanisms by which it causes disease, and other complex problems of amebiasis. The use of these axenic cultures led to the first direct evidence that the therapeutic action of tetracycline in amebiasis is specifically on the amebae and not on the associated bacteria.

A highlight of research on amebiasis was a successful pilot study which the drug clefamide proved effective as an easily administered therapeutic and preventive agent against amebiasis. A tablespoon of syrup containing a small amount of the drug was given twice weekly for a year to 25 percent of the people in a hyperendemic area of Mexico. Most of those receiving the drug lost their infections and remained protected against reinfection; the untreated people continued to show the usual infection level for the village.

Another highlight was the promise shown by Ciba 32,644 Ba, a nitrothiazole derivative, against both amebic dysentery and amebic liver abscess, even when the two conditions occurred together. A drug that is effective against both amebic intestinal and tissue infections is urgently needed.

Two diagnostic tests for amebiasis were developed: (1) a gel-diffusion precipitin test for both amebic liver abscess and acute amebic dysentery, and (2) a fluorescent antibody test for amebiasis, using two widely differing strains of amebae as antigen.

Toxoplasmosis

A diagnostic test was also one of the important results of research on toxoplasmosis, a parasitic disease that causes birth defects, eye disease, and myocarditis. The test pinpoints antibodies present in the acute stage of both congenital and acquired toxoxplasmosis. Prompt diagnosis of the acute stage of the disease in the newborn is important; only if therapy is started early can there be hope of preventing extensive tissue destruction by the parasite and possible crippling results such as mental retardation and blindness.

Two experimental drugs for treating toxoplasmosis brought encouraging results when tested in mice. The animals survived infection after treatment with Trimethoprim and Ro 4–4393 and a combination of these drugs.

Other research

In research on other parasitic diseases, investigators opened the way to a possible vaccine against Chagas' disease, which is estimated to affect 7 million people in South America. The one-celled organisms that cause the disease were incubated in a culture containing mitomycin C or actinomycin D. When inoculated into mice, these treated parasites produced an immunity that protected the animals against lethal, untreated parasites.

Other investigators made what my well be an important contribution to the Nation's economy by developing a way for food animals—such as cattle, pigs, and sheep—to be vaccinated against nematode worms. They developed methods for growing the worms in culture. Antigenic material extracted from cultured larvae produced a solid immunity when injected into domestic animals.

Investigators reported 21 new cases in the United States of human infections with filarial worms, a family that includes the common heartworm of dogs. The mosquito-transmitted infections were acquired in the South, mostly in Florida.

Dermal leishmaniasis is a disease characterized by ulceration of exposed parts of the body. *Leishmania mexicana*, the parasite that causes the disease in Central America (where it is widespread), was found to be transmitted by the sand fly

Phlebotomus flaviscutellatus. This discovery of the natural vector paves the way for possible control measures.

FUNGAL DISEASES

In research on fungal diseases, bats were firmly linked to histoplasmosis, a systemic infection that, in the severe form, is usually fatal and, in the benign form, affects many millions.

In 1965, investigators of the Middle America Research Unit of the Institute and the Walter Reed Institute of Research were the first to isolate *Histoplasma capsulatum*, the organism causing the disease, from the feces of naturally infected bats. During the past year, this work was confirmed by one group of investigators who, in addition, demonstrated that a widespread species of bat—the Mexican free-tailed type common in the Western and Southwestern United States—can be infected with histoplasmosis. Further confirmation was supplied by other investigators who, for the first time, found the disease in western Texas in Mexican free-tailed bats.

H. capsulatum was also isolated from a brown house bat captured in Maryland.

The possibility that bats with their wide migratory and feeding habits, may serve as vectors for the dissemination of *H. capsulatum* assumes real epidemiologic and public health importance.

In other noteworthy results of research in fungal diseases, the antifungal antibiotic Saramycin demonstrated impressive therapeutic effect against experimental infections in animals, and an Institute scientist prepared a World Health Orgnization document that threw fresh light on the prevalence of fungal diseases in Africa.

RICKETTSIAL DISEASES

A team of grant-supported research physicians reported that thrombocytopenia (a decrease in the number of blood platelets, which are essential to normal blood clotting) occurs frequently in Rocky Mountain spotted fever and that outbreaks in families are a significant aspect of the disease. These findings are important contributions to the differential diagnosis of a disease that, sometimes confused with meningococcemia (invasion of the bloodstream by meningococci), should be speedily diagnosed because fatality is about 20 percent in the absence of prompt specific therapy.

Intramural scientists continued active in sponsoring investigations in Egypt and Ethiopia on the occurrence of epidemic typhus in such domestic animals as the camel and donkey. The demonstration that such animals are susceptible to typhus and are involved in its epidemiology provided important new information necessary for the control of the disease.

RESEARCH HIGHLIGHTS OF 1966

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

To single out research highlights from the more than 2000 grants and contracts funded by the National Institute of General Medical Sciences in some 50 scientific disciplines could be misleading unless the reader understands that, for each highlight selected and described briefly in this report, there are numerous others of great significance.

The scientific areas to which the Institute provides the greatest support are, broadly speaking: biophysical, biochemical, biological, and medical.

Biophysical sciences

The application of engineering principles and techniques to biomedical problems is called biomedical engineering. Once limited mainly to instrumentaton, this field is now one of the broadest, most dynamic in medicine, embracing communication and control in living systems.

For example, electrical engineers and scientists at the Case Institute of Technology are studying methods for restoring activities of muscles and nerves damaged by disease or accident. Their tools are minute electronic devices that can be implanted in muscles and tissues. The devices contain FM transmitters smaller than an aspirin tablet with circuitry scarcely visible to the naked eye.

Using methods similar to those employed in "jumping" tangled communications lines downed by storms, the Case engineers are programming their instruments to bypass damaged nerves and to reactivate paralyzed limbs.

Dr. Wen H. Ko and his Case Institute associates also are developing and perfecting extremely small electronic implant systems to monitor heart beat, blood pressure, and other internal functions vital to the study of disease. Microelectronic systems that can control automatically various parts of the body, including heart, bladder, and nervous system have enormous potential for victims of stroke and other disabilities. An implant in one of the laboratory animals at Case already has stimulated muscle movement, a major development toward rehabilitating amputees through electronics.

Up to now, these implants have been either battery- or radio-powered. Dr. Ko and his associates are now experimenting with piezoelectric energy derived from the body itself by the motion of the blood flowing through the arteries. Dr. Ko has developed a device that could possibly keep a heart pacemaker running 20 years without batteries. The device, an implanted ceramic wafer, is designed to generate continuing power from the impact of the heart beat.

Pioneering in the use of ultrasound for diagnostic purposes, an investigator at the Albert Einstein College of Medicine has applied ultrasonography to research in diseases of the eye. He has studied "acoustic profiles" of normal eye tissues in experimental animals and in man and has compared them to profiles of diseased tissues. These studies have already resulted in the diagnosis of eye tumors that had escaped previous detection. All indications are that further research will lead to even wider application of ultrasonic techniques to the diagnosis of eye diseases.

At the University of California (Berkeley), a scanner-computer system is being developed which will automatically analyze biological and medical specimens in diagnosing diseases at an earlier stage than is now possible.

Under the direction of a Nobel Prize laureate, the major effort on this project has been in developing the actual equipment. Some preliminary studies, however, using automatic methods have identified bacterial species. In collaboration with scientists at the University of California School of Medicine in San Francisco, clinical application is beng made of this scanner-computer technique in identifying disease-producing organisms. The scientists will continue development of this technique not only for early dagnosis of diseases, but also for determining the most effective drug for combating a disease once it has been identified.

Certain tumors become resistant to radiation treatment when oxygen, removed from surrounding tissue by ordinary metabolic processes, is not replaced by the blood. A method for treating these anoxic tumors may develop from investigations being conducted at the Yale University School of Medicine. Researchers are trying to find an agent that will sensitize the tumor to radiation, as oxygen does, but that will not be metabolized. The Yale investigators have found certain organic nitroxide compounds which seem to sensitize malignant tumors in animals and are now investigating the metabolism of these agents in the tissues.

Microwave radiation is increasing in the environment as more powerful microwave tubes and transmitters are used in television and other communications systems, for transportation safety devices like radar, and in many aspects of national defense. Industry and the armed forces, recognizing that such radiation can be hazardous to health, have established safe limits of field intensity above which technicians and others should not be exposed.

The precise biological effects of microwave radiation, however, have yet to be explained. At Tufts University School of Medicine, investigators are trying to determine how microwave radiation affects man and his environment. The investigators have observed cell irregularities occurring in irradiated rabbit eyes, unusual muscle damage in rabbits suffering radiation burns, and cell aberrations in irradiated corn seedlings. Also attributed to microwave radiation are a lengthened pupation period and a decreased adult life span in insects. Irradiated chick embryos showed retarded growth and suppressed differentation in the brain, eye, and, in some cases, in limited blood development.

Johns Hopkins University scientists, working on the broad subject of nuclear instrumentation and chemistry in medicine, have developed a new technique in the study and treatment of pulmonary emphysema. The new technique, and improved method of radioisotope scanning and chest radiography, bids in determining the degree of involvement of the lungs, and in following the progress of the disease. The investigators are now exploring the possibility that this lung scanning technique could help in the early diagnosis of lung cancer.

Several years ago, Dr. Albert Szent-Gyorgyi, Nobel Prize laureate for his work in isolating and characterizing Vitamin C, observed that certain tissue extracts

promoted, while others retarded, growth of transplanted or spontaneous tumors in mice. When partially purified preparations were subjected to infrared analysis, they showed the presence of a ketoaldehyde of a type not previously found in living organisms. This discovery was very important in itself, a major step toward unraveling the complexities of the body's chemical systems.

Dr. Szent-Gyorgyi and his associates are now energetically studying the chemical structure and biological properties of the glyoxal derivative which they had discovered and named retine. They have already found that retine inhibits the synthesis of proteins by cells, although it does not interfere with formation of nucleic acids. It is hoped that these studies will lead to a detailed knowledge of a hitherto unknown regulatory mechanism, knowledge that could lead to a better understanding of the way organisms control normal growth and cell division. This information, in turn, will provide a better basis for the rational control of abnormal growth, such as cancer.

Biochemical sciences

Biochemical sciences supported by the Institute include studies of basic life processes as well as studies of ways of predicting hazards in drugs and of preventing or at least minimizing their toxic effects.

The possible connection between the anesthetic Halothane and a fatal liver disorder was the subject of an intensive survey completed during the past year. The National Halothane Study, which exonerated the anesthetic, was conducted by the National Academy of Sciences' National Research Council under a contract with the Institute. The study was prompted by reports in 1963 of isolated cases of death associated with liver damage following Halothane anesthesia which, until then, had been credited with an impressive safety record and had many other advantages.

An analysis of records of anesthetic administration to more than 856,000 patients revealed fatal massive liver damage in 82 instances, or less than one in 10,000 operations. Contributing to those fatal disorders could have been factors such as shock, overwhelming infection, congestive heart failure, or preexisting liver disease. The study established that massive fatal liver damage following anesthesia is rare and is not significantly associated with any single anesthetic practice.

The Institute's pharmacology and toxicology program is trying to define ways in which anesthetics and other drugs affect body functions and organs. Other questions are: How to improve the correlation between the effects of a drug on laboratory animals used in testing and its effects on patients? What dosages will be toxic or produce undesirable effects? What undesirable effects may occur when two or more drugs are used together? Such questions underlie the research supported by the pharmacology and toxicology program.

Toxicological and pharmacological studies of drugs are usually first tested on healthy animals. But patients are not healthy; they are suffering from diseases of one sort or another. A more reliable evaluation of a drug may be obtained by administering it to animals which have the same disease against which the drug might be used in man.

At the University of Iowa, one attempt at refining test systems for evaluating drug toxicity is being made by developing what are called model disease states in laboratory animals, that is, diseases that are similar to those in man. So far the researchers at the University of Iowa have induced renal disease, neurogenic disease, and endocrine disorders in several animal species. Possible variations in the activity and toxicity of drugs may be revealed in the environment of a particular disease.

Investigators at Emory University Medical School in Atlanta have shown that the action of an anti-cancer drug on tumors in hamsters, mice and rats is improved when the animals' bodies are cooled and the tumors kept at normal temperatures. In an experiment with 75 hamsters, the scientists lowered the animals' body temperatures to 40 degrees Fahrenheit but the tumors were kept at the precooling stage of 96 degrees. As the scientists describe it—"Cool hamster, warm tumor." Keeping the tumor at normal temperature while the rest of the body is cooled is achieved by electric heating, application of infrared, or application of ultrasound, the method used depending upon the size of the tumor. Then five-fluorouracil, an anti-cancer drug, was injected into the animals' veins. After an hour, the hamsters' normal body temperatures were restored. All lived and 20 days later their tumors were gone. When the same amount of drug was given tumor-bearing animals at normal body temperature, the tumors continued to grow.

Not all toxicological effects are caused by drugs or other chemicals induced into the body; disease itself causes various chemical changes in the body. Now, investigators at the Pacific Northwest Research Foundation in Seattle are expanding upon this basic principle by studying through x-ray spectography the effects of metallic elements on body tissues and fluids. Their research is expected to yield valuable new information on 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.

Research supported by the Institute in the field of organic chemistry is producing new kinds of molecules designed to fight disease, including one type of molecule active against influenza virus. The goal of these projects is to synthesize appropriate molecules which will have specific, limited, and predictable effects in a biological system with a minimum of other kinds of actions. Some of the most important recent work in this area is the synthesis of a variety of "cage" type molecules. It was a related molecule, amantadine, which was found to be active against the influenza virus under certain conditions. One investigator has synthesized an amantadine-type nucleus and is preparing a variety of derivatives of this structure for biological testing.

The Institute supports research on the encoded mysteries of the primary genetic substances, RNA (ribonucleic acid) and DNA (desoxyribonucleic acid).

During the past year a scientist at Cornell University determined the exact structure of one of the transfer RNA molecules, among the smallest nucleic acids in nature. A major achievement, this development of an analytical method will make it possible to determine the structure of similar and more complex key nucleic acids and perhaps to construct specific biological molecules to order.

Recent advances in chemical genetics—the study of the chemical nature of genetic material and the consequences of its alteration—can contribute much toward combating diseases of genetic origin. Dr. Victor A. McKusick, one of the Institute's grantees at Johns Hopkins University, has listed in his book "Mendelian Inheritance in Man" some 500 diseases and disabilities which are traceable to genetic factors, an indication of the extensive role genetics plays in health and disease.

To understand the function of the genetic material it is necessary to elucidate its chemical structure. The Institute has a collaborative research project with Oak Ridge National Laboratory to study methods for separating certain protein molecules and for developing new methods of producing the biological materials needed for genetics research.

Biological sciences

During the past year, the Institute held a conference of prominent physicians and professors from this country and abroad to help identify the critical areas in genetics research and to analyze the problems impeding research progress. The conference recommendations will be used to expand the genetics research program in the future.

Genetic abnormalities are sometimes revealed by abnormal numbers of chromosomes in body cells and the slow process of counting chromosomes is a serious bottleneck in genetics research. Therefore, the Institute is supporting a project at the National Biomedical Research Foundation, Silver Spring, Md., which not only can speed chromosome counting but can gather and analyze other data more rapidy. The project is developing a device which automatically scans photographs and, in conjunction with a computer, analyzes quantitatively the information on the photograph. A special technique emphasizing fine details will be used to obtain data from pictures of chromosomes, neurones, and other materials.

As in the business world, important progress in medical research must often depend on superior production methods for highly specialized materials needed in the research of many scientists. Such methods are given top priorities by this Institute.

For example, a grantee of this Institute at Columbia University, Dr. Samuel Graff, is producing large quantities of Interferon and supplying it to the National Institutes of Health and other laboratories. The real payoff will come when Interferon, a virus-fighting substance, can be used in medical treatment.

Treating humans with Interferon thus far has been impractical because the substance is "species specific"—that is, Interferon produced in mouse tissue protects only mice from viral infections, rabbit Interferon protects only rabbits, and so on.

When production of human Interferon is achieved—and responsible scientists predict that day soon may come—Interferon can prove to be one of the most important medical discoveries of the 20th Century.

If Interferon's early promise is upheld, it may be employed effectively against every virus disease, including the common cold. If it should be established clinically that cancer is virus-related, Interferon also may prove to be one of the most effective anti-cancer agents ever discovered.

Medical sciences

The Institute's medical sciences programs are concerned with the clinical application of basic biochemical and biophysical investigations. Emphasis is on anesthesiology, surgery, diagnostic radiology, and pathology.

A project at Duke University is seeking a reliable method for selecting donors for clinical homotransplantation of tissues and organs. The body's rejection of transplants is still the greatest hindrance to successful tissue and organ transplantation. The Duke project is studying various "tissue typing" methods for detecting antigenic incompatibilities between donors and patients. The tests have enabled investigators to predict survival times in 50 of 51 skin grafts carried out among siblings. Further refinements are being made in the tests to permit selecting donors unrelated to the patient. Such information may be vital to any organ transplant program.

During the year, the Institute's anesthesiology research program expanded rapidly, stimulated by funds provided by the Congress for the concerted attack on heart disease, cancer, and stroke. In Fiscal Year 1966 the Institute supported 27 anesthesiology research projects, compared to 16 in Fiscal Year 1965. The anesthesia research includes basic research on how anesthetics function in the body, the development of better and safer methods of anesthesia, the management of respiration, the control and relief of pain, and improvement generally of surgical patients.

New instrumentation and computer techniques are being used at Northwestern University in experiments with methods of correcting breathing difficulties in patients after surgery. The investigator has devised a way to measure air flow in postoperative patients and, through a computer, to diagnose respiratory difficulties accurately and rapidly.

In other anesthesia research supported by the Institute, scientists are working on drugs that will be not only effective anesthetics but will ensure adequate blood flow to the brain and other vital organs during surgery. A device to monitor the volume and velocity of blood flow within the veins and arteries has been developed at the University of Washington by a team of engineers, physiologists, and anesthesiologists. Called the Doppler flowmeter, it is small and portable and produces measurements as auditory signals. The next step is to perfect the device so its output can be fed into a computer, thereby greatly facilitating patient monitoring during surgery.

At the University of Pennsylvania a team of scientists studying the effects of commonly used drugs on the heart and blood vessels, have observed that though the strength of the heart beat diminishes considerably during general anesthesia, blood circulation does not become dangerously low. The investigators have identified many of the compensatory mechanisms the body uses to keep an adequate supply of blood circulating despite a weakened heart beat. These findings will help anesthesiologists give safe, effective anesthesia without fear of dangerous depression of the circulation.

These examples of research projects indicate to some extent the diversity and breadth of the research base which this Institute provides for biomedical science.

CHILD HEALTH AND HUMAN DEVELOPMENT

TREATMENT FOR RH HEMOLYTIC DISEASE

Progress has been made in recent years in the management of erythroblastosis fetalis. Caused by an incompatibility of blood between the mother and fetus, the condition is responsible for a large number of deaths among newborns. When the mother's blood is Rh-negative and the father's Rh-positive, the fetus that results from this union is often Rh-positive. Late in the first pregnancy, some of the Rh-positive blood from the fetus crosses the placenta to enter the mother's blood. Between the first and second pregnancy, the mother's blood may build up anti-Rh antibodies. During second and subsequent pregnancies these maternal Rh antibodies may attack and destroy the Rh-positive blood cells in the fetus.

In severe cases, when the baby's life is in danger, he can be saved by exchange transfusions, which substitute Rh-negative blood for that being destroyed by the antibodies. At other times the obstetrician must weigh the risk of fetal death from Rh-incompatibility against the risk of neonatal death from prematurity should he decide to interrupt the pregnancy. Previously, the decision has been made on the basis of individual factors including the past history of the patient, estimated fetal weight, and levels of maternal Rh-antibody. In recent years, spectrophotometric scanning of amniotic fluid has been added as a more precise method of assessing risk in deciding when to interfere with the pregnancy.

During the past year, an NICHD grantee in New York summarized his success in using a new technique to reduce fetal deaths in Rh-isoimmunized pregnancies. In this technique, called amniocentesis, some of the amniotic fluid surrounding the fetus is withdrawn and analyzed by spectrophotometric scanning of the pigments in the fluid. This analysis gives an assessment of the current state of the fetus in terms of danger of death or probable survival which is not possible from maternal blood tests. If the spectrophotometric tracing indicates that the fetus is in danger, the baby can be delivered early and transfusions of Rh-negative blood can be given to save him. If the scan doesn't indicate danger, then the baby can be allowed to go to full term. The procedure has the advantage of signaling the need for pregnancy intervention and transfusions.

In about 400 pregnancies where Rh was a problem and amniocentesis was used in selected cases, perinatal loss (stillbirths plus neonatal death) was 9 percent of the total number of Rh-affected babies. When amniocentesis was not used in the management of Rh-sensitized pregnancies, perinatal loss due to Rh was 30 percent of the total number of Rh-affected babies.

Still another procedure has proved helpful where hemolytic disease develops in a fetus too premature for delivery. In this case, the investigators have gone one step further than amniocentesis and have given blood transfusions to the fetus while it is still in the uterus. Although the investigators have had surprising success with this technique, it is used only in those cases where there is no other hope.

Another approach to the Rh-sensitization problem is to prevent its occurrence. Several Institute grantees, as well as scientists in England and Germany, have found that administration of anti-Rh antibody gamma globulin to the mother within a few hours after delivery of the first baby prevents the formation of antibodies.

Although these studies on an immunizing agent are in the preliminary stages, virtually total protection has been achieved in more than 250 women in clinical trials. The use of this agent promises to eliminate Rh incompatibility as a factor in infant mortality.

SUDDEN INFANT DEATH

Each year approximately 10,000 to 20,000 infants in the United States die suddenly for no apparent reason. A leading cause of death in children under one year of age, this mysterious killer, also called "crib death," strikes apparently healthy, well-nourished infants, often with no previous record of illness. Doctor's don't understand it, and until now they had little but their own experience to draw upon for the answers.

Now, the NICHD has published the first book-length treatment of this subject, based on a conference where the leading investigators and authorities on "crib deaths" pooled their knowledge and ideas for the first time. The book, *Sudden Death in Infants*, explores the mysterious syndrome from the viewpoints of eminent pediatricians, pathologists, microbiologists, and other scientists from the United States and Europe. Prior to publication, a comprehensive bibliography was compiled through 1965 and added to the book.

Several points of agreement among the conferees are set down in *Sudden Death in Infants*, although the studies they report show a wide divergence of approach to the problem. Suffocation, long thought to be the cause, has been virtually eliminated as a possibility.

The book has implications beyond the mere recording of accumulated knowledge. By clarifying the problem of sudden infant deaths, and by publicizing an interchange not only between men but between disciplines, *Sudden Death in Infants* is the definitive work in its field and promises to be the springboard for expanding research and cooperation among scientists.

A recent contract between the NICHD and Children's Hospital Research Foundation of the District of Columbia calls for investigations of many possible

causes of this syndrome. Other Institute-supported research is continuing to investigate the various avenues of approach to this problem.

For example, investigators in Seattle, Washington are making a thorough study of all the sudden, unexplained deaths among infants in Kings County and some from surrounding counties. Of 155 sudden, unexpected infant deaths examined to date, 115 have remained unexplained. All of these 115 deaths occurred during the sleep period. The study has also shown that the peak incidence of sudden infant deaths is 2–4 months of age. The mysterious syndrome spares very young infants and is rare after 6 months of age.

EFFECT OF OXYGEN SUPPLY OF FETUS

Premature birth is associated with a high rate of disease and congenital malformations. To find out more about the causes of prematurity and ways of preventing both the premature birth and its aftermaths, NICHD grantees in Denver have initiated a broad-based program to study several aspects of pregnancy.

Among the hazards of pregnancy, both to mother and fetus, are chronic vascular hypertension and renal disease in the mother. These conditions are often associated with toxemia, an accumulation of waste products which can lead to death of the fetus and the mother. Toxemia occurs in 6 to 7 percent of all pregnancies and accounts for about one-third of maternal deaths and at least 30,000 stillbirths or neonatal deaths each year in the United States.

Toxemia of pregnancy is accompanied by an insufficient supply of oxygen to the fetus. In this regard, the work of the Denver investigators may be helpful in alleviating the condition.

Using pregnant sheep, the investigators found that a quick change of altitude, from 5,280 feet (Denver) to 12,700 feet (top of Mt. Evans) resulted in some rather dramatic and startling effects on the oxygen supply to the fetus. Because of a marked loss of oxygen in blood of the mother, there was insufficient oxygen for the fetus, and some of the infants failed to survive. On the basis of these studies, the physicians have recommended against overnight travel of pregnant women from a low to a very high altitude.

Continuing their studies, the researcher found that administration of extra oxygen to pregnant sheep helped the fetus compensate for lack of oxygen. They plan to determine whether the human fetus will also benefit from the administration of extra oxygen to the mother.

INTRAUTERINE CONCEPTIVE DEVICES

One inexpensive and reliable aid to birth control, which has shown promise in recent years, is the intrauterine device (IUD), a simple plastic or metal device that can be left inside the uterus for long periods of time.

These devices, which must be put in place by a physician, are usually made of plastic and are shaped like bows, loops or spirals. All these devices seem to have little effect on uterine function except to prevent conception. They sometimes cause bleeding or discomfort and are occasionally expelled. Also, the mechanism of their contraceptive action is not known.

Scientists at the Department of Agriculture's Research Service, under a contract with NICHD, are studying the contraceptive action of IUD's and their effect on surrounding tissues. In their initial investigations, they found that IUD's interfere with different phases of reproduction in cattle, sheep and pigs.

For example, the spiral IUD placed in the uterine horn of ewes interferes with normal sperm transport into the oviducts. This is also true in cattle. However, the mechanism of action in these two animals is different. In the cattle, the interference is apparently mechanical obstruction of sperm because if a spiral is placed in one uterine horn fertilization sometimes took place in the opposite horn. In the ewe, the interference may be more than mechanical since no fertilization could be detected in either oviduct regardless of which uterine horn the spiral was placed.

In the pig, the IUD does not prevent fertilization but inhibits embyro survival with embryo dying at 8–14 days after fertilization.

In addition, a grantee at the University of California reported that in the Macaque monkey the presence of an intrauterine device was associated with rapid discharge of ova from the tube into the uterus so that implantation could not occur. Sperm migration remained unimpaired.

FAMILY PLANNING PRACTICES

The recent introduction of new methods of fertility control is creating rapidly changing patterns of family planning practices among the American population. The Institute last year awarded a contract to a Princeton University research team to study fertility control practices of American families. The investigators have just published preliminary results of the survey, which reports the results of detailed interviews with 5,600 married women under age 55.

Based on the information from this sample of the population, these investigators estimate that 6.4 million women have used the "pill" one time or other and an addtiional 4.7 million indicate they may use it in the future. They also estimate that approximately 3.8 million married women under age 45 and living with their husband are currently using the oral contraceptive.

As might be expected, use of the oral contraceptive is much greater among younger than older women. The proportion of married women under 25 who currently use the pill or have only temporarily stopped using it was 40 percent. Thirty percent of wives under 25 were currently using the pill, compared with only 5 percent of those under 40.

Not all women use the oral contraceptives for contraceptive purposes. They are also used for the relief of menstrual discomforts, for regulation of the ovulatory cycle—frequently with the intent of promoting a subsequent conception—and for many other purely medical purposes.

Data in this preliminary study include use of oral conceptive by age, parity (number of live births), color, religion and education.

The complete survey includes a national sample of 6,200 married women between the ages of 18 and 54. The survey includes questions about sources of family planning information, birth control methods, and side effects. Socioeconomic level of family, age, time of menopause and other such basic facts are also being recorded. The results will provide important baseline data from which other studies, geared more specifically to health problems, can be formulated.

The study will form a sequel to two Growth of American Family surveys conducted in 1955 and 1960 and will be the first intensive survey of fertility control practices since the introduction of the oral contraceptive in 1960.

CHROMOSOMAL ABNORMALITIES

Chromosomes are the structures in the nucleus of the cell which carry the genes. Gross abnormalities of cromosomes are one cause of spontaneous abortions and birth defects, including mental retardation, in humans. An estimated 1 out of every 150–200 live births results in a chromosomal abnormality. The cause of these abnormalities are generally unknown and some of their effects are lethal.

Researchers supported by the NICHD at the University of Colorado are examining evidence that human sex chromosome defects may not occur by chance, but are due to specific environmental factors.

Beginning in 1963, these scientists have surveyed 7,000 newborns in Denver, Colorado. They found that babies with abnormal numbers of sex chromosomes tended to appear in seasonal clusters (during a five-month spring and summer period).

In the first two years of the survey, they found an incidence of sex chromosome aberrations of 0.6 percent during one five-month period. No aberrations occurred in similar populations either before or after this period. There was also an elevated incidence of Down's syndrome (mongolism) during this same five-month period.

During the past two years, they found another cluster of sex chromosome aberrations in a five-month period with a seasonal distribution similar to that in the first cluster. These findings suggest that X chromosomes (sex chromosomes) and autosome No. 21 (the chromosome involved in mongolism) may be equally susceptible to production of abnormalities due to some external factors, though the particular environmental factors involved are still to be identified. The Colorado researchers are currently looking into the possibility that a latent virus infection in the mother around the time of conception may be one factor involved.

Another NICHD grantee at the Michael Reese Hospital and Medical Center, Chicago, Illinois, found clusters of chromosomal abnormalities about the same time as those found by the Denver group.

Congenital defects appearing in the two clusters, totaling 11 births, were of the type caused by autosome defects. Further study by the Chicago group showed

a number of deaths occurred among babies conceived at the same time as those with chromosomal defects.

Since German measles (rubella) and infectious hepatitis in particular are suspected of causing chromosome aberrations, these grantees studied the occurrence of infectious diseases in Chicago during the times abnormal babies were conceived. However, only a significant increase in common measles (rubeola) was found during the first cluster. Studies to date fail to support the role of rubeola as a cause of chromosome changes noted in these newborns. This group is continuing its studies of chromosome aberrations and extending them to investigate stillbirth and spontaneous abortion populations.

In addition, scientists at the NICHD's Biomedical Sciences Laboratory are studying spontaneous abortion material in a search for viruses that may cause cell changes leading to gross chromosomal abnormalities that can be lethal to the embryo.

THE PHENYLKETONURIC CHILD AND DEVELOPMENT

The successful dietary treatment of phenylketonuria (PKU) has shown that mental retardation caused by this inborn metabolic error can be alleviated. However, much remains to be learned about the future needs of the children with this condition.

NICHD grantees at the University of Colorado Medical Center, Denver, are conducting longitudinal research on the development of PKU children in order to determine their particular needs for continuing therapy and special schooling if they are to achieve adequate intellectual and physical development. They are studying phenylketonurics who were treated from birth and those in whom treatment was started late.

Some of their findings show:

(1) A high incidence of non-localized minimal neurologic deficits appear in PKU children regardless of when therapy begins, and there appears to be a trend toward a higher incidence of neurologic dysfunctions in children when treatment is begun after 3 months of age;

(2) Even when PKU children are treated ideally (therapy begun early and well controlled) their IQ scores fall below the ranges established for their parents or non-PKU siblings;

(3) Language development is delayed in all PKU patients in which treatment was begun late, but patients treated early also show some delay of vocalization to language skills;

And, (4) Six patients receiving dietary treatment begun at 9 weeks of age, when taken off the diet at age 3 to 4 years, appeared to have no adverse effects with respect to scores on IQ tests. However, children whose therapy began late, while showing no adverse changes on their IQ scores, did evidence behavioral changes such as increased hyperactivity, tremors and restless sleeping, and the parents said they became "more difficult to handle."

The Colorado team utilizes developmental intelligence tests, neurological evaluations, electroencephalograms, physical growth checks, and speech and hearing evaluations in its long-term studies of PKU children.

In addition, the team's psychologist, social worker and others are looking into the child's home environment for any factors that may have a bearing on the child's progress and are studying the parents to determine inherited capacities of children.

Diet treated phenylketonurics in the study are followed with weekly serum phenylalanine level checks, reports of illnesses, and dietary intake records during the first year of life. From 1 to 5 years of age, monthly checks are made and annually thereafter.

The investigators expect their studies to yield important data to help determine the long-term therapy requirements of PKU children, plan special education programs, and identify any minimal impairment of these children which might be amenable to therapy.

DERMATOGLYPHICS AND DIAGNOSIS OF PRE-BIRTH DAMAGE

Dermatoglyphics (finger, palm and sole prints) have been seen to be abnormal in a number of clinical disorders including certain chromosome defects.

An NICHD-supported reseacher at the University of Minnesota in Minneapolis has been conducting dermatoglyphic studies in three types of mental retardation not associated with obvious chromosomal errors. The three types were: phenylketonurics, representing a genetically determined type; rubella-damaged

individuals, representing an environmentally induced type; and idiopathic retardates, whose mental retardation may have resulted from genetic or environmental factors, or both.

The Minneapolis study showed that the phenylketonurics and idiopathic retardates differed very little in dermatoglyphic characteristics from a group of mentally normal controls.

The rubella-damaged group did exhibit abnormal dermatoglyphic patterns, including increased frequency of transitional and simian palmar flexion creases, of whorl patterns on the finger tips, and a tendency toward more palmar patterns than normal.

In this project, although differences noted were significant, their magnitude was not sufficient to allow them to serve as an effective diagnostic aid. However, the implication of the results are that an environmental agent, like rubella virus, may damage the fetus early in gestation and cause changes in finger, palm and sole prints that could be easily detected at birth. Thus, dermatoglyphics may prove a useful tool for identifying damage occurring during the intrauterine period that is not associated with chromosomal errors.

DIAGNOSTIC COUNSELING

The Children's Diagnostic and study Unit of the Institute's Mental Retardation Program is a diagnostic clinic serving dependents of military personnel eligible to receive care at the U.S. Naval Hospital in Bethesda, Maryland.

One part of the research program is directed toward the problem of parent counseling and its effect on the child diagnosed as mentally retarded. Researchers at this NICHD clinic are studying how well parents understand their retarded children and how this understanding is affected by diagnostic counseling. This research is based on the premise that a retarded child's parents can manage the child better and plan for his future more accurately if they are given all necessary diagnostic, prognostic and program information available regarding their child.

To date, several trends have emerged from this continuing study: (1) parents are usually accurate in estimating their child's present abilities, but poor in estimating the future social adaptability of their child; (2) certain "styles" of counseling do promote better parental estimates of their child's future social adaptation; (3) parents who do not accurately estimate their child's present abilities are less successful managers of the child; (4) parents often see their child's difficulties in terms of many separate little problems—poor speech or poor motor coordination— both of which are amenable to therapy; and (5) counselors sometimes reinforce parental views of retardation as the sum of many little problems by talking to them about the child as if his retardation were the sum of separate handicaps.

The clinic's staff recognizes that two major limitations confront the counselor trying to help parents manage their retarded child better. One limitation—parental—involves errors resulting from the particular outlook of the parents which can promote misunderstandings in relating necessary information to the counselor. The second limitation—a counseling one— involves the degree to which the counselor uses the most effective "style" to give parents information. Both limitations are important since errors in information parents give or in counseling, if combined, can seriously impede efforts to insure the retarded child a future place in adult society.

CULTURAL AND ENVIRONMENTAL RETARDATION

Severe retardation is often caused by metabolic errors or chromosomal defects. However, the effects of cultural and environmental conditions can cause mild retardation which accounts for a high proportion of all retardation in America. Since this type of retardation contributes to the self-perpetuating nature of disadvantaged groups in society, ways to combat it must be found.

NICHD-supported educators and psychologists from the University of Kansas are attempting to find the best ways to educate and train the deprived urban child and his family. One approach they are using is to study the parent-child interactions in preschool training.

They have found that when the preschool child is given a choice between playing with dolls, blocks, etc. and taking a "lesson," given by the mothers themselves, the children will select at least one lesson a day. Indeed, some children are selecting to repeat the same lesson at least five times a day.

In order to investigate the potential of this approach to education, the Kansas group began a parent-child interaction program in 1965. At first teachers worked with mothers at home; then this was expanded to a cooperative nursery program to provide greater training opportunites for the mothers in the project. Finally the mothers, after appropriate instruction, began trying to teach their own children many of the skills necessary for later achievement upon entering school.

The mothers in this study used 106 special lesson "kits" prepared by the Kansas City investigators. They were taught to give the children special attention, smiles, praise and other signs of approval to reinforce a child's progress during a lesson. These methods were encouraged in place of progress gained through threats, nagging and the like. When the mother was teaching her own child, although the incidence of praise increased, she could not stop nagging her own offspring. This year, the mothers are teaching children other than their own and the incidence of nagging has almost literally disappeared. Now, the children choose the mother to teach the lesson they select and appear to enjoy learning more.

The Kansas City researchers are confident that parent-child teaching and training, such as that demonstrated in their program, may be one answer to breaking the self-perpetuating cycle of cultural "deprivation." They feel that the application of the findings in this study will not only help remedy current learning deficits of these children but prevent further deficits from occurring through the improved mother-child interactions.

Cultural and environmental conditions which contribute to school failure and functional mental retardation can be combatted through incentive techniques in remedial instruction programs. Educators have often noted the difficulty in motvating children from culturally deprived families. The same University of Kansas investigators running the parent-child interaction program have set up a program to investigate motivations for academic achievement.

In this study, children who attend remedial instruction courses, after regular school or work, are given classroom tasks within their realm of ability. They are given a variety of incentives for achievement. Also, they must show gradual improvement over the year to continue receiving incentive awards.

The students are given incentive points for doing homework and for grades earned in regular school classes. These points can then be traded in for such things as daily snacks, field trips, picnics, toys, or clothing when enough are accumulated. During the first year of this program, the pupils from a sixth grade remedial classroom showed significant academic progress with the grade average for the entire group being raised from D to C.

Public school achievement test scores for this same group showed they had gained 1½ years during the year compared to only a 6-month gain in the two years prior to remedial class attendance. A group from the same area, not enrolled in this program, showed only 0.8 years gained on the achievement test and only 0.2 of a grade point gain in school marks.

Utilizing a similar incentive program, these same researchers ran a remedial classroom for junior high school drop-outs who were members of the local Neighborhood Youth Corps.

These students were motivated to achieve by being paid for each problem worked correctly in class.

Pre- and post-achievement tests in this group showed an average gain of 1.3 years in only two months of instruction compared to an average 0.2 years gain for Neighborhood Youth Corps children working at regular jobs and not attending classes.

SENSORY AND MOTOR DISORDERS AND LEARNING

Mental retardation is associated with impairment of an individual's adaptive behavior. Impaired adaptive behavior may be reflected in maturation, learning and/or social adjustment. Learning problems, in particular, range from difficulties in the acquisition of simple skills, such as self feeding, to more complex symbolic and abstract learning problems encountered during the school years.

Since learning depends greatly on sensory and motor input, these systems must be sound to assure an effective learning experience.

In school, many children are slow learners because of poor performance secondary to various sensory and motor deficits. For example, children with cerebral palsy, having poor motor coordination, may not do well in school, and some of the mental retardation associated with cerebral palsy may actually be impaired learning ability due to poor motor coordination.

While completely deaf, blind or mute children have their handicaps recognized and, hopefully, compensated for in the school environment, those with partial or subtle impairments of sight, hearing and speech are not always recognized. Often their learning difficulties are simply attributed to limited intellectual ability or to a lack of effort. With better diagnostic and remedial instruction techniques, these children can be saved a lot of misery and be helped to achieve their full intellectual potential.

NICHD grantees at the Albert Einstein College of Medicine, New York City, have developed a series of tests aimed at helping to recognize partial impairments affecting learning. These tests check the child's auditory-visual, visual-touch, and visual-motor activities and their ability to integrate these important sensory-motor activities.

The Einstein investigators' auditory-visual integration test involves the child listening to a series of taps, and then matching up what he hears with a series of dots on paper. Through this test, the Einstein group has shown that reading disabilities seem to reflect an interference with auditory-visual interaction. They have also found that even though retarded readers are poor at auditory-visual integration, this is not the sole factor involved in their disability. They note that this type of sensory integration in its more complex and general form may be one process underlying adaptive behavior and thus IQ. They found that individuals who can perceive and integrate many sensations, such as touch, vision, and hearing, are very likely to be the more "intelligent" ones.

This continuing research is based on the principle that each sensory system in the body interacts with and is modified by other sensory systems and that even the simplest sensory functions are continuously modified by activity in the other senses. The Einstein researchers believe that, in humans, integration of sensory systems is a developmental process which follows a definite age and growth curve.

INFANTS' VISUAL PERCEPTION

The long-held belief that infants' eyes are too immature to see anything but brightness, color and size has been challenged by an investigator supported by NICHD at Western Reserve University in Cleveland.

Studying hundreds of infants, the investigator found that from birth babies consistently choose to look at patterns rather than at blank squares or colors—which means they actually can see the patterns. In collecting data, the investigator devised an ingenious method of peering into the pupils of babies' eyes and observing the reflections there. When he saw an image fixed directly on the pupil, he surmised that the baby was seeing the picture. He concluded that whether or not the picture means anything to the infant is irrelevant, the important point being that he has an innate, unlearned interest in patterns.

While newborns appear to be most attracted by linear arrangements, checkerboards or stripes, the interest at three months of age shifts to a more complex, random pattern. It is believed this is due to learning or maturation of the brain. The preference for patterns seems logical when one considers that the child later finds his way around the environment by the shape of things rather than by their color.

GROWTH PROBLEMS AND CONGENITAL HEART DISEASE

A new approach to the problem of growth retardation in children with congenital heart disease is indicated by the recent findings of an NICHD-supported study of the physiology of normal and abnormal growth.

A team of investigators composed of biochemists, endocrinologists, cardiologists, physiologists and psychologists working at Johns Hopkins University is studying many parameters of growth in normal children, in children with retarded growth due to a variety of causes, and in children with congenital heart disease showing "recovery" growth spurts after cardiac surgery. Preliminary data from this project concern muscle growth in normal and abnormal states. Muscle normally grows in mass through cell multiplication and through increase in individual cell size. Experiments in animals have shown that poor nutrition affects chiefly the growth of individual muscle cells rather than the cell multiplication process, resulting in small cells but a normal number. On the other hand, children with pituitary insufficiency were found to have a deficiency of cell number. Human growth hormone caused a response of cell multiplication and a spurt in growth. Studies of children retarded in growth as a result of congenital heart disease demonstrated a reduced muscle cell population, with normal cell size. These results suggest that poor nutrition in these patients is not the chief cause

of poor growth. Further studies which delineate the endocrine status of these cases may clarify further the nature of their growth retardation.

DEVELOPMENT OF MORAL BEHAVIOR

Research leading to the identification of how youngsters develop particular codes of moral and ethical behavior is of great interest not only to the Institute but to the behavioral science community at large. In one study of factors influential in moral development, investigators supported by NICHD have correlated specific motivational factors with resulting moral behavior.

Studying nursery, kindergarten and school age children, these investigators on the Berkeley campus of the University of California report findings which indicate important sex differences in the motives underlying moral behavior. Utilizing a situation in which school age subjects could easily cheat or resist the temptation to cheat, boys and girls differed greatly in the apparent reasons for their behavior. In general, it appears that cheating is correlated with maladjustment and low social status among boys. Among girls, however, cheating seems to be part of a constellation of variable indicative of a high attainment motivation and a need to be accepted and popular with other girls.

The thrust of this continuing study will be to identify patterns of parental behavior which are associated with moral development in children.

NUTRITION STUDY OF TEENAGERS

According to the results of another NICHD-supported project, a nutrition study among teenagers, the youth of America are less obese than is commonly thought: only 11 percent of a group of typical California high school students were found to have what is considered "excess" body fat. But the national concern about overweight was evidenced quite markedly among teenagers—60 percent of this same group thought they should lose weight. The study also confirmed that teenagers in this automated age do not get enough exercise. The far-reaching impact of this study, however, lies in the great wealth of information gained. Based on this information, the investigators believe that workable programs of weight control and physical fitness among teenagers could be implemented on a sound basis in the communities of America.

The investigators in this project studied approximately 1,000 teenagers, an entire grade of the public high school system in Berkeley, California. They began studying the youngsters in the ninth grade and continued through the twelfth. Their aim was to gather as much information as possible about teenagers' attitudes and interests in matters of desirable body conformation, choice of diet, meal preference and types of activity favored. In addition, they collected objective anthropometric data on body composition. Certain identifiable patterns emerged offering practical implications for program planning in weight control and physical fitness. And, encouragingly enough, the youngsters showed a continuing high level of interest in their body conformation and in methods of changing it to more nearly match their ideals.

Another interesting result of this study is the pinpointing of differences in attitudes toward nutrition between children from different social strata. This finding will allow nutritionists and physical fitness personnel to tailor programs to meet the needs of all children regardless of economic level or social status. In the past, such programs—aimed squarely at the middle class—have been discriminatory against both the poor and the rich.

MOLECULAR AGING

Much of the structure of the human body consists of giant molecules that are replaced slowly. Over the decades of human life changes occur in these molecules. However, the details of these chemical alterations and the mechanisms underlying them are still incompletely understood.

Many scientists, including NICHD-supported biochemists at the Albert Einstein College of Medicine are studying the structure of collagen, one of the giant molecules of the body that shows molecular changes with age.

Collagen is the major protein constituent of the supportive tissues and accounts for about one third of the total amount of protein in the body. It is found in skin, blood vessels, tendon, and bone, and it forms the supporting network of fibers in which most body tissues and organs rest.

Collagen consists of long linear molecules connected to each other by cross-links. These links give the protein stability and affect its physical and chemical properties.

Scientists know that the number of cross-links between collagen fibers increase as the body ages. This multiplication of cross-links is probably responsible for the changing properties of collagen with age. However, the nature of these links and the factors influencing their formation and breakdown have been unclear.

Two years ago, the NICHD-supported biochemists at Albert Einstein found certain chemical groups in collagen that might be involved in the cross-linkage process.

Now, the biochemists have isolated four of these groups and have identified two of them chemically. One compound the scientists have named enosaline. The enosaline on one collagen molecule can react chemically with the enosaline on a neighboring collagen molecule to form a paired compound that makes a firm structural link between the strands. The researchers have also developed procedures for locating the cross-links under the electron microscope and have shown that they occur at the ends of the collagen molecules.

These findings are an important step in understanding the structure and biosynthesis of the body's structural proteins and the changes which occur in them with maturation, aging and disease. Collagen is of great interest, for changes in the amount and character of collagen are apparent in diseases commonly associated with the elderly, such as arteriosclerosis, osteoporosis, pulmonary fibrosis, and even the wrinkled sagging skin of the very old. Understanding the biochemistry of collagen opens pathways to the study of how drugs and environmental factors can modify collagen structure.

ENVIRONMENTAL EFFECTS ON AGING

Although most gerontologists feel that the maximum lifespan of an organism is genetically determined, they would also insist that the environment has a great influence in determining the actual lifespan.

At NICHD's Gerontology Branch, rotifers are being used to explore the relative effect of heredity and environment on the lifespan of an animal. Rotifers, tiny organisms 1/50th of an inch in diameter, live in pond water and dine on algae, and have a normal lifespan of 18–20 days. Like other living organisms, the rotifer goes through periods of infancy, growth, and aging, and thus offers researchers the opportunity to study, in a shortened period of time, what happens during the entire lifespan of an organism.

By altering the environment of the rotifer, the NICHD biologists found they could more than double the normal lifespan of this creature. Notably, however, one change in the environment affected the rotifers at one stage of life, while another affected a different stage.

The scientists observed that lowering the level of nutrition increased total lifespan by lengthening the period of growth and development. Restricting the rotifers' diet greatly increased their egg-producing days, but did not affect the post-egg-producing period, which remained constant regardless of diet.

However, reducing the water temperature affected the rotifers' post-egg-producing period. A reduction of water temperature by 18 degrees Fahrenheit increased the animals' total lifespan by lengthening their "senior years," but had no effect on the growth period.

These findings suggest that it may be possible to delay aging without affecting the period of growth and development, by slowing down the process in the later years of life. They demonstrate the extent to which environmental influences may modify the lifespan of some species of animals and indicate that it may be possible to increase longevity further by manipulating our surroundings.

LEARNING AND AGE

Researchers interested in psychological processes in the aged have long recognized that the elderly experience more difficulty in learning than their younger associates. A recent series of studies at Duke University's Center for the Study of Aging and Human Development has shown that this learning deficit of older people isn't as great as generally believed. This NICHD-supported research has demonstrated that the elderly learn nearly as well as their younger companions but because of increasing anxiety may refuse to respond.

The scientists at Duke considered learning as actually encompassing two processes: the acquisition of information, and performance involving the use of this

information in response to some stimulus. Test results showed that older people seem to be hampered in the latter, or performance, aspect of the process.

When the investigator asked groups of aged (60 plus) and younger (under 50) groups to learn lists of words flashed at 4-second intervals, the younger subjects did better. At 8-second intervals, however, the older group showed dramatic improvement, while response of the younger group improved only slightly. Notably, improvement in the older group was in reduction of errors of omission, not errors of commission, indicating that the difference in learning ability was in the failure of the oldsters to respond, not in their reduced ability to learn.

Significantly, when given 8 seconds in which to respond, the older group responded within 4 seconds, just as the younger group did. With the pressure of time removed, the older group learned almost as well and responded just as rapidly as their younger testmates.

Physiological signs of increased stress added evidence to the concept that anxiety had blocked the response capacity of the oldsters. Blood levels of free fatty acids, an index of anxiety, were higher in the older group and reacted differently to the strain of the learning process.

Free fatty acid levels rose in both young and old subjects during the learning task. However, they were higher in the old subjects at the start of the task, remained higher throughout the task, and took longer to return to their original levels. This persistent heightened arousal could well make learning more difficult for the aging individual, causing a vicious spiral of increased stress and increased relative task complexity. The researcher believes that because of the increased stress involved in the learning process, older people may subconsciously disengage themselves from the learning task.

DIABETES IN OLD AGE

A major problem facing scientists is the distinction between physiological changes in the human systems caused by aging and changes caused by diseases of the same systems with advancing age. Often it is difficult to determine which changes should be classified as diseases, which as the normal processes of old age.

Diabetes mellitus is an example of this problem. An essential part of the diagnosis of diabetes is high blood sugar levels. In recent years, however, it has been noted that if standard diagnostic levels are used, almost 50 percent of people over 40 would have to be labelled diabetic.

As an aid in studying this problem, scientists at NICHD's Gerontology Branch have developed a new technique for precise control of the level of blood sugar in humans. Normally, blood sugar levels are controlled by the body's insulin response to sugar. All sugars are broken to the simple sugar, glucose, and then converted through the action of insulin, to glycogen and stored principally in the liver for future use. The new control technique is based on an externally applied system which overrides the body's own control mechanisms, allowing the external regulation of blood sugar levels.

Using this technique, the investigators have developed a broader understanding of the body's intrinsic response to sugar. They noted that young adults require about twice as much sugar as older subjects to produce comparable blood sugar levels. Moreover, the increase in the amount of sugar and the rate of administration required to maintain high blood sugar levels was smaller in the older group. This demonstrates that the ability to convert sugar to glycogen decreases with age.

Continuing these studies, the NICHD investigators hope to provide more insight into the relationship of diabetes and old age. At present, diagnostic standards and appropriate diabetic therapy in older patients are based upon an inadequate understanding of the impact of age on the body's response to sugar. With the use of their newly developed technique, the researchers are establishing accurate insulin response data and are defining age differences in man. With a broader understanding of this problem of aging, new standards can be established and a better program of treatment can be developed.

NATIONAL SUPPORT FOR PERFORMANCE OF MEDICAL AND HEALTH-RELATED RESEARCH BY SOURCE OF FUNDS, FISCAL YEARS

[In millions of dollars]

Source of funds	1961	1962	1963	1964	1965	1966	1967
	Actual					Estimate	
Total	$1,045	$1,290	$1,486	$1,652	$1,841	$2,050	$2,275
Government	604	819	964	1,099	1,229	1,380	1,540
Federal	574	782	919	1,049	1,174	1,319	1,475
State and local	30	37	45	50	55	61	65
Industry	312	336	375	400	450	500	560
Private support	129	135	147	153	162	170	175
Foundations and health agencies	77	78	85	88	92	95	98
Other private contributions	15	18	21	22	25	28	29
Endowment	19	19	19	19	19	19	19
Institutions' own funds	18	20	22	24	26	28	29

NOTES

The estimates of national support for medical and health-related research shown above update the series extending back to 1947 published in Resources Analysis Memorandum No. 7 "National Time Series on Support of Medical and Health-Related Research—The Years Since 1947." 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 nonindustrial 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. RAM No. 7 also presents a detailed discussion of the definitions and statistical methodology underlying the time series.

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.

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 1966 and 1967 may therefore overstate the Federal share.

Federal support for performance of medical and health-related research, fiscal year 1964–67 [1]

[Thousands of dollars]

Agency	1964 actual			1965 actual			1966 actual			1967 estimate		
	Total	Budgeted	Directly related	Total	Budgeted	Directly related	Total	Budgeted	Directly related	Total	Budgeted	Directly related
Total	$1,048,661	$843,044	$205,617	$1,174,208	$927,625	$246,583	$1,318,722	$1,046,991	$271,731	$1,475,485	$1,192,036	$283,449
Atomic Energy Commission	78,056	7,514	70,542	84,585	7,827	76,758	89,588	8,017	81,571	95,449	8,614	86,835
Federal Aviation Agency	2,939	2,939		2,798	2,798		2,496	2,496		2,690	2,690	
National Aeronautics and Space Administration	41,200		41,200	60,000		60,000	75,352		75,352	79,925		79,925
National Science Foundation	23,145		23,145	19,678		19,678	13,812		13,812	14,408		14,408
Tennessee Valley Authority	385		385	554		554	945		945	1,546		1,546
Veterans' Administration	33,153	33,153		36,907	36,907		46,673	46,673		46,923	46,923	
Department of Agriculture	27,911		27,911	40,470		40,470	44,661		44,661	45,732		45,732
Department of Commerce	409	51	358	366	33	333	344		344	394		394
Department of Defense	86,484	46,869	39,615	101,261	53,461	47,800	119,153	67,465	51,688	114,281	64,080	50,201
Department of Health, Education, and Welfare	752,535	751,824	711	826,200	825,828	372	928,293	926,877	1,416	1,070,617	1,068,137	2,480
Public Health Service	(721,835)	(721,835)		(781,849)	(781,849)		(882,264)	(882,264)		(1,017,764)	(1,017,764)	
NIH	(651,010)	(651,010)		(715,072)	(715,072)		(790,927)	(790,927)		(813,895)	(813,895)	
NIMH [2]										(102,471)	(102,471)	
Other	(30,700)	(29,989)	(711)	(44,351)	(43,979)	(372)	(46,029)	(44,613)	(1,416)	(52,853)	(50,373)	(2,480)
Department of the Interior	1,750		1,750	618		618	1,942		1,942	1,928		1,928
Department of State	694	694		771	771		1,463	1,463		1,592	1,592	

[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 Jan. 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 Science 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 reflect these transfers.

NOTE.—The statistics shown above—actual obligations for fiscal years 1964, 1965, 1966, and estimates for 1967—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 research 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, programed and justified as such, and supported for the purpose of improving human health (all the research activities of agencies or subagencies 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 percent 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 the following "Resources for Medical Research" report: Rept. No. 4 presents data for 1947 through 1961 inclusive; "Resources Analsysis Memo No. 7" presents data for 1962 and 1963. These publications together with the revised data shown above for 1964–66, constitute the definitive time series on Federal support for the performance of medical and health-related research in the postwar period. A more comprehensive analysis of recent trends will be published shortly in the "Resources for Medical Research" series.

DIVISION OF BIOLOGICAL STANDARDS

WITNESSES

DR. RODERICK MURRAY, DIRECTOR, DIVISION OF BIOLOGICS STANDARDS

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

GEORGE A. BRUST, EXECUTIVE OFFICER, DIVISION OF BIOLOGICS STANDARDS

MRS. ELIZABETH GRUBBS, BUDGET OFFICER, DIVISION OF BIOLOGICS STANDARDS

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. WILLIAM H. STEWART, SURGEON GENERAL

G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER

JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	2,039	2,323	2,338
11.3	Positions other than permanent	27	37	37
11.5	Other personnel compensation	61	47	47
	Total personnel compensation	2,127	2,407	2,422
12.0	Personnel benefits	204	232	234
21.0	Travel and transportation of persons	109	118	118
22.0	Transportation of things	7	10	10
23.0	Rent, communications, and utilities	40	51	51
24.0	Printing and reproduction	5	8	8
25.1	Other services	389	457	274
	Project contracts	580	1,975	2,275
25.3	Payment to "National Institutes of Health management fund"	1,356	1,708	1,892
26.0	Supplies and materials	810	958	928
31.0	Equipment	98	558	439
	Subtotal	5,725	8,482	8,651
95.0	Quarters and subsistence charges	−2	−2	−2
99.0	Total obligations	5,723	8,480	8,649

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	295	333	333
Full-time equivalent of other positions	6	6	6
Average number of all employees	275	293	296
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Program by activities:			
	Biologic standards (program costs, funded) [1]	5,530	8,480	8,649
	Change in selected resources [2]	193		
10	Total obligations	5,723	8,480	8,649
	Financing:			
16	Comparative transfer from other accounts	−467	−805	
25	Unobligated balance lapsing	1,550	229	
40	New obligational authority (appropriation)	6,806	7,904	8,649
	Relation of obligations to expenditures:			
10	Total obligations	5,723	8,480	8,649
70	Receipts and other offsets (items 11-17)	−467	−805	
71	Obligations affecting expenditures	5,256	7,675	8,649
72	Obligated balance, start of year	761	1,087	1,959
74	Obligated balance, end of year	−1,087	−1,959	−3,559
77	Adjustments in expired accounts	−34		
90	Expenditures	4,896	6,803	7,049

[1] Includes capital outlay as follows: 1966, $105,000; 1967, $558,000; 1968, $439,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $572,000; 1966, $765,000; 1967, $765,000; 1968, $765,000.

Mr. FLOOD. We now have with us Dr. Roderick Murray, Director of the Division of Biologics Standards.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

We have a biographical sketch of Dr. Murray which we will insert in the record at this time. You are a long way from home, aren't you, Doctor? You still managed to get to Harvard, I see.

(The sketch follows:)

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., Univ. of Witwatersrand, South Africa, 1930; M.Sc., Univ. of South Africa, 1931; M.D., Harvard Medical School, 1941.

Experience: 1956–present: Director, Division of Biologics Standards.
1949–1956: Asst. Chief, Laboratory of Biologics Control, NIH.
1947–1949: Laboratory 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: Asst. 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 Assoc.; American Public Health Assoc. (Fellow); American Assoc. of Immunologists; American Academy of Microbiology (Fellow).

Special awards, citations, or publications: Cullen Medal, Faculty of Science, Univ. of Witwatersrand, 1931; Alpha Omega Alpha; Distinguished Service Medal USPHS, 1965. Thirty-nine publications.

Mr. FLOOD. You have a statement, Doctor, but before you begin that, have you any of your staff that you might want to introduce so we will know who they are?

Dr. MURRAY. Mr. Brust, on my left, who is executive officer of the Division; and Mrs. Grubbs, who is the budget officer.

Mr. FLOOD. How do you want to proceed?

Dr. MURRAY. I would prefer to read my statement, if you will indulge me.

GENERAL STATEMENT

Dr. MURRAY. It is again a pleasure to appear before you on behalf of the Division of Biologics Standards. First, I would like to outline, if I may, the function of the Division.

FUNCTION OF THE DIVISION

The Division is responsible for establishing and maintaining standards of quality and safety of all biological products that come within the jurisdiction of the Public Health Service. The term "biological product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives applicable to the prevention, treatment, or cure of diseases or injuries of man. These products include all vaccines, antitoxins, therapeutic serums, allergenic products, and human blood for transfusion, as well as products prepared from human blood.

Because many of these products are derived from living organisms, such as bacteria and viruses, and all by their nature are either potentially dangerous or ineffective if improperly prepared and tested, close surveillance of production and a constant effort to improve quality are essential. The development of realistic standards for these products and the exercise of proper control over them can be effective only if backed by an active research program of sufficient flexibility to provide information needed for the formulation of such standards.

Since most biological products cannot be standardized by chemical or physical means, their strength or potency must be tested in relation to established standard or reference preparations.

Mr. FLOOD. What is a reference preparation?

Dr. MURRAY. It is a preparation of the same type, which has been set aside and portions of it are always run in parallel.

Many of the comparisons must be carried out in animal tests. In order to establish uniformity of potency of these products, the Division provides manufacturers, and others engaged in biologics standardization, with these standard or reference preparations.

Mr. FLOOD. What do you mean by provide?

Dr. MURRAY. They are issued on request.

Mr. FLOOD. At no cost to the applicant?

Dr. MURRAY. At no cost to the applicant. This is part of the job of control.

IMPLEMENTATION OF FUNCTION

The basic instrument for the control of biological products provided in the Public Health Service Act is that of licensing. The legal requirement is that a license may be issued only upon a showing that standards designed to insure the continued safety, purity, and potency of the product have been met. Both the product and the manufacturer must be licensed. Once an establishment has been licensed, it is inspected each year, frequently by a team of as many as three Division scientists,

to determine continued compliance with standards. In addition, each manufacturer must submit to the Division, for testing and review, samples and test reports of each batch or lot of the product he proposes to distribute. Test reports are checked; samples are tested when necessary, and the lot in question is not distributed until a letter of authorization is issued by the Division. There are a few products for which this procedure is not deemed necessary to insure their safety, purity, and potency.

In general, there have been few problems of enforcement with the large producing laboratories because of the realization that in matters concerning safety and potency of biological products, the public interest is also the interest of the manufacturer.

Mr. FLOOD. In general?

Dr. MURRAY. Yes.

Mr. FLOOD. What would be an exception? I do not expect you to name the firms but what would be an exception?

Dr. MURRAY. I think the exceptions are minor, inadvertent and not intentional.

Moreover, the severity of the penalty which can be exerted—the suspension or revocation of the license—could put an establishment out of business.

With its ultimate objective the protection of the public against unsafe and ineffective biological products of an inherently complex nature—the Division is often confronted with problems which may never be completely solvable. The most successful accomplishments of the Division are represented by those occasions where difficulties are anticipated, headed off, or abated.

Mr. FLOOD. How do you enforce them when you have to, by injunction in the Federal district court?

Dr. MURRAY. Usually, as far as the safety and potency of these products are concerned these facts are determined prior to the time the products get on the market, in which case the issue is stopped.

Mr. FLOOD. I was thinking of the *Rand* case.

Dr. MURRAY. There it was a disregard of instructions not to ship, in which case the procedure is to secure an injunction. If the establishment were licensed this would have been cause to revoke the license.

Mr. FLOOD. By the way, is there an established procedure to revoke a license?

Dr. MURRAY. Yes. There can be a temporary revocation.

Mr. FLOOD. With a right of hearing?

Dr. MURRAY. Yes, with a right to have a hearing. The procedures are set up in the regulations of the Public Health Service.

Mr. FLOOD. Is there an appeal from a revocation action?

Dr. MURRAY. In those instances they would also follow the provisions of the Administrative Procedures Act.

The Division necessarily maintains an active interest in products which have long since been routinely accepted by the medical and health professions, and in some instances even forgotten by the majority of scientists working in the field. The development of new products, however, which is inevitably accompanied by technical problems, necessarily commands the most attention of both the control and research facilities of the Division. The aim is to make possible the early application of these products to public health and medical practice, while

assuring conformance to the highest standards for safety and potency on the basis of current knowledge. As the body of scientific knowledge grows, standards for biological products must be adjusted to the more refined "state of the art." Also, the implications of advancing knowledge must be studied in relation to biologics. For example, data on the phenomenon of virus-induced tumor formation in animals under special circumstances has stimulated work on the significance of these observations in regard to viral vaccines for human use.

RESEARCH

The research activities of the Division cut across many disciplines and fields of interest. New and important techniques in immunochemistry must be explored in relation to investigations on the induction of antibodies by vaccines, the measurement of various types of antibodies, the relation of the antibodies to protection, and the relation of cellular mechanisms as well as antibodies to the entire defense mechanisms of the body. New techniques in virology, for example, have placed Division scientists in the vanguard of knowledge of such subjects as viral oncogenesis and means of measuring attenuation of virus strains for the preparation of vaccines.

Mr. FLOOD. Do you get into the area of molecular attraction?

Dr. MURRAY. Eventually we will get there but that is not part of the picture at the moment.

The Division's competence in electron and fluorescent microscopy is being exploited to characterize viruses and associated viral-like particles, and to research for covert viral agents in tissue cultures used for the growth of viruses.

Advances in virology, especially, are moving rapidly toward the development of new viral vaccines for mumps, parainfluenza, rubella, respiratory syncytial illnesses, and other diseases.

Mr. FLOOD. Do you touch on the widespread hope of a vaccine for cancer?

Dr. MURRAY. This would not be our primary interest but if the state of knowledge got to the point where it looked as if a vaccine for cancer or for a form of cancer was in the works, we would have to be working with it in order to know what standards should be applicable in the event this became a useful product. I think that is our main function, to be ahead and develop the standards.

The unique features of each of these vaccines—the pathogenicity of the virus; the culture system; the techniques for inactivation and assuring absence of adventitious agents; the tests for safety, lack of communicability, and freedom from neurovirulence—require intensive study and the attention of an expert staff.

RUBELLA VACCINE

Division scientists must be constantly aware of advances in research, and design their own research activities in preparation for control and testing problems which inevitably arise before new biologic products can be entered into general use. Because their work toward these goals often provides leads, DBS scientists, occasionally produce an experimental immunogenic agent. This happened recently when Division scientists developed the first experimental live attenuated rubella vaccine.

Mr. FLOOD. Was that an accident?

Dr. MURRAY. No; because the virus of rubella had been isolated and scientists were working with it and because we knew there would be tremendous interest, that somebody would come up with a vaccine in the near future. Members of our staff were studying what would have to be done in order to provide standards for a vaccine were it developed by anybody. The Division is not in the business of developing vaccines. This is a side effort in the process of providing standards.

Their investigative work on the characteristics of the vaccine is continuing with very good progress. The vaccine has been distributed to interested researchers in the scientific community as well as to the National Institute of Allergy and Infectious Diseases, in order that it may receive maximum exposure. It is anticipated that a safe and effective rubella vaccine will be available to the public within a reasonable time.

The same Division research team has recently developed a simple, rapid, and inexpensive hemagglutination inhibition test for rubella antibodies. It is presently engaged in perfecting this test, the widespread use of which could speed the development of rubella vaccine.

Mr. FLOOD. Could these vaccines develop blood clots?

Dr. MURRAY. No. The hemagglutination inhibition test is a test that uses red cells from chickens and if the virus is present it will agglutinate the blood cells.

ONCOGENIC FACTORS IN RELATION TO VACCINES

Another important facet of the Division's research program is the study of the oncogenesis of viruses, and the significance of present knowledge in this field relative to the safety of viral products. A considerable portion of the program is organized in contractual projects to extend the work being done in the Division's own laboratories. This contract program covers aspects that are of special importance to biologics. Other organizations are, of course, pursuing this important subject from many other standpoints.

Division scientists are concentrating on developing methods for the detection of tumor viruses. Special techniques must be devised to reveal covert or latent viruses. This is of special importance to vaccine development. Viruses must be grown on living cells, for example, in animals, eggs, or tissue cell culture. Even if a virus itself is nononcogenic, the culture system may contain covert agents. These agents may grow very slowly in the culture, if at all, producing no discernible effect on the culture cells. Techniques, such as immunofluorescence or the use of certain types of metabolic inhibitors, are being explored to see if these will help in revealing their presence. Electron microscopy is used to search for virus-like particles in concentrated preparations of tissue culture material.

There is no evidence, at this time from scientific observations and experience with long-established biological products, that their use bears any relation to tumorigenesis in human beings.

Mr. FLOOD. No evidence?

Dr. MURRAY. From the ones that are used at present.

Mr. FLOOD. A long established biological product, though, might be the key. I have heard it suggested that the new birth control pills are suspected of producing tumors.

Dr. MURRAY. I am glad I do not have to pass judgment on that, sir.

Mr. FLOOD. Well, I am glad you are glad. That is fine.

Dr. MURRAY. Nevertheless, because of the likelihood that, in the years to come, many new viral vaccines will be developed in new tissue culture systems, it is essential that the Division have firmly established knowledge and research competence in this field.

Mr. FLOOD. By new tissue culture systems do you mean human tissues?

Dr. MURRAY. A variety of tissues. Ultimately human tissues may be used.

Mr. FLOOD. Are they not used now?

Dr. MURRAY. Only experimentally. There is talk of using baboon tissues and tissues from other animals. Duck embryo looks like it might be useful.

PROGRAM PLANS

The Division's contract program on oncogenesis is just beginning. It will be expanded in scope and content to include testing of additional biological products, screening of suspect materials for covert viruses by presently available techniques and the development of new ones. Means will be sought for determining oncogenic effects more rapidly than is now possible. The study of the ingredients of plastics will be extended to determine possible oncogenic effects as well as the deleterious effects already observed on blood reagents. The 1968 budget contains a request for an additional $300,000 to extend the contract program on oncogenicity.

Mr. FLOOD. Does this get in the area of asbestos and beryllium and plastics? There was some reference to that yesterday.

Dr. MURRAY. No. Plastics are being widely used for containers of various kinds and the composition of the plastics is never constant. This poses problems because materials leach out of the plastics and have deleterious effects on the product, particularly in the case of small containers.

Dr. STEWART. Mr. Chairman, the reference to plastics yesterday was to the solvents used in making plastics.

Dr. MURRAY. There are areas of research on biologics in which impediments to progress exist. To some extent, the impediments are economic. This is true of rarely used products such as botulism type E antitoxin, antivenin for coral snake bites, and trichinosis antigen. Economic impediments, as represented by the investment required for research to develop and produce a product for prospective markets, also exist for some of the arbovirus vaccines. While the development of such products for general use is usually outside the focus of the Division's principal responsibility, nevertheless, the need for their development is recognized. For example, the Division has available for emergencies a standard antitoxin preparation for botulism type E. Similar standards are being sought for coral snake antivenins.

The Division personnel are gradually moving into the extended quarters as they become available with the completion of the annex to building 29. Funds in the amount of $175,000 are being requested to equip the renovated space in building 29. In addition, $85,000 is requested for procuring specialized equipment, such as an electron microscope.

In conclusion, the request of the Division of Biologics Standards for 1968 is $8,649,000 compared with $8,480,000 available in 1967.

I shall be glad to attempt to answer any questions you may have.

SUMMARY OF BUDGET REQUEST FOR BIOLOGICS STANDARDS

Mr. FLOOD. There is a small decrease here of $60,000 in the budget for this item, from $8,709,000 for 1967 to $8,649,000 for 1968. However, there is an expansion of the program because there is a decrease of $805,000 for what this appropriation will be assessed to support what we call the management fund. Is that so?

Dr. MURRAY. There is an adjustment on account of the management fund but the apparent decrease is largely due to the fact the 1967 budget had nonrecurring items in it.

UNOBLIGATED BALANCE

Mr. FLOOD. Well, what did you have to cut back in order to come up with this "Unobligated balance, reserve" of $229,000?

Mr. CARDWELL. The $229,000, Mr. Chairman, relates to the 1967 cutback programs that we have discussed previously. It has to do with restrictions on procurement of equipment, supplies, travel, and reproduction.

Mr. FLOOD. This much comes out of his hide?

Mr. CARDWELL. Yes.

RESEARCH ON TUMOR PRODUCING AGENTS

Mr. FLOOD. You are asking for an increase of $300,000 for research on tumor producing agents?

Dr. MURRAY. Yes.

Mr. FLOOD. Can you tell me how much you spent on this in 1966?

Mr. BRUST. This year it is $1,837,000.

Mr. FLOOD I want to know what you spent in 1966.

Mr. BRUST. In 1966 we spent $555,000, and in 1967 we are expecting to obligate $1,837,000.

Mr. FLOOD. What happened to make it necessary to expand this program?

Dr. MURRAY. This started in 1966 on a limited scale. It is difficult to get contractors in this field; to be sure there is no duplication and that there are contractors who will do the work needed. Thus in 1966 there was a lapse of funds for this reason and that is why the amount spent in 1966 appears small whereas in 1967 we are getting up to the amount of money we originally projected would be needed to mount this program, and the additional $300,000 will, in our opinion, be what is needed to round out the program.

Mr. FLOOD. These are all contracts?

Dr. MURRAY. Yes.

Mr. FLOOD. You said you could not find contractors.

Dr. MURRAY. During the time that the money was available to us, which was a matter of 8 or 9 months.

Dr. SHANNON. We only had this time to develop it. Our apportionment for that year came through the beginning of October.

Mr. FLOOD. What about your old line activities? What problems have you had in connection with your old line activities since last year? Have you had any trouble?

Dr. MURRAY. I do not think so.

Mr. FLOOD. You remember Harry Truman used to say "Never forget your old friends." What about your old activities?

Dr. MURRAY. We are continuing very actively in the area of old line products such as typhoid vaccine.

Mr. FLOOD. Is there any tuberculosis vaccine?

Dr. MURRAY. We are not doing any developmental work on tuberculosis vaccine. BCG is available as a licensed product. We also have an active interest in cholera vaccine and at the moment there is interest in trying to improve such old line items as smallpox vaccine, not only by ourselves but by others.

Mr. FLOOD. Cholera? When was the last case we identified stateside?

Dr. MURRAY. It is not an important vaccine in the United States but it is very important for travelers who go abroad.

Dr. SHANNON. That is particularly true of the armed services.

Mr. FLOOD. It flares up pretty regularly, too.

Dr. MURRAY. And there is an interest on our part in improving the plague vaccine which is being used in southeast Asia.

Mr. FLOOD. In direct ratio to the speed of transportation your problems increase, do they not?

Dr. MURRAY. I would think everybody's problems increase in relation to transportation.

Mr. FLOOD. But you still have the same incubation period no matter how fast the jet travels.

Dr. MURRAY. That is right. The use of these agents, particularly the smallpox vaccine, in trying to prevent smallpox from coming in the country, is really the concern of——

Mr. FLOOD. How often should you vaccinate for smallpox?

Dr. MURRAY. Some people say children should never be vaccinated in this country.

Mr. FLOOD. Some people say what?

Dr. MURRAY. That it should not be used because smallpox has not appeared in this country since 1946 and there are side effects in some persons following vaccination.

Mr. FLOOD. I am speaking of travelers.

Dr. MURRAY. Travelers should be vaccinated. That is a requirement.

Mr. FLOOD. Every year?

Dr. MURRAY. Quarantine requirements are every 3 years. Recently the Public Health Service had inhouse requirements for every year for some of its personnel.

Mr. FLOOD. Do not the boys in the Air Force have it every year?

Dr. MURRAY. I do not know what the requirements are but they get more than their share of inoculations.

Mr. FLOOD. I have heard that mentioned.

Thank you very much.

Dr. MURRAY. Thank you very much.

JUSTIFICATION MATERIAL

Biologics Standards

Amounts available for obligation

	1967	1968
Appropriation	$7,904,000	$8,649,000
Comparative transfers within NIH accounts	805,000	0
Total	8,709,000	8,649,000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Biologics standards (total obligations)	333	$8,480,000	333	$8,649,000	0	+$169,000
Unobligated balance, reserve		229,000		0		−229,000
Total, obligations and balance	333	8,709,000	333	8,649,000	0	−60,000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	333	333	0
Full-time equivalent of other positions	6	6	0
Average number of all employees	293	296	+3
11 Personnel compensation:			
Permanent positions	$2,323,000	$2,338,000	+$15,000
Positions other than permanent	37,000	37,000	0
Other personnel compensation	47,000	47,000	0
Total personnel compensation	2,407,000	2,422,000	+15,000
12 Personnel benefits	232,000	234,000	+2,000
21 Travel and transportation of persons	118,000	118,000	0
22 Transportation of things	10,000	10,000	0
23 Rent, communications, and utilities	51,000	51,000	0
24 Printing and reproduction	8,000	8,000	0
25 Other services	457,000	274,000	−183,000
Project contracts	1,975,000	2,275,000	+300,000
Payment to "National Institutes of Health management fund"	1,708,000	1,892,000	+184,000
26 Supplies and materials	958,000	928,000	−30,000
31 Equipment	558,000	439,000	−119,000
Subtotal	8,482,000	8,651,000	+169,000
Quarters and subsistence charges	−2,000	−2,000	0
Total obligations by object	8,480,000	8,649,000	+169,000

Summary of changes

1967 enacted appropriation	$7,904,000
Comparative transfers with NIH accounts	805,000
Unobligated balance, reserve	−229,000
1967 total estimated obligations	8,480,000
1968 estimated obligations	8,649,000
Total change	+169,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in:				
1. Annualization of new positions authorized in 1967				$23,000
2. Annualization of wage board pay raise				1,000
B. Program:				
1. Oncogenic research	12	$1,600,000		300,000
2. Equipment and other objects		592,000		260,000
Payment to "National Institutes of Health management fund" for centrally furnished services		1,708,000		184,000
DECREASES				
A. 1 less day of pay in 1968 (261 days in 1967, 260 days in 1968)				−7,000
B. Equipment and other objects				−592,000
Total net change requested				+169,000

EXPLANATION OF CHANGES

Direct operations.—The program increase of $560,000 will provide $300,000 for research contracts to further the Division's efforts in solving problems concerned with oncogenic (tumor-producing) factors as they relate to the safety of vaccines; $175,000 for equipping renovated space and $85,000 for specialized research equipment.

Explanation of transfer

	1967 estimate	Purpose
Comparative transfer from other NIH accounts	+$805,000	Redistribution of the "National Institutes of Health management fund."

Significant items in House and Senate Appropriation Committee reports

ITEM: 1967 SENATE REPORT

(1) The committee is disappointed by the delay in expanding the Division's work on the disturbing problem of the tumor-producing effects of viral vaccines for which the Congress made an additional $400,000 available last year. The committee will expect this program to be in full operation by the time of next year's hearings. (page 38)

ACTION TAKEN OR TO BE TAKEN

(1) As outlined in the narrative justification, the Division is striving to resolve various problems of oncogenesis in relation to biological products and is mounting a realistic contracts program to meet its needs.

Biologics standards

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	333	$2,639,000	333	$2,656,000	0	+$17,000
Other expenses		5,841,000		5,993,000		+152,000
Total	333	8,480,000	333	8,649,000	0	+169,000

INTRODUCTION

The Division of Biologics Standards (DBS) is responsible for assuring the standards of potency and safety of a variety of immunizing agents and diagnostic and therapeutic biological products including blood and blood products for use in human beings. "Potency" means that the products are indeed capable of eliciting the bodily reactions or other effects that they are purported to do. "Safety" means that they will exercise their prophylactic, diagnostic or therapeutic effect without inducing undue toxic reactions in the individuals to whom they are administered.

The Division's mission encompasses two objectives:

1) Development of standards and requirements, incorporating the necessary guidelines for potency and safety, for biological products to be administered to the general public by practitioners of medicine. The Division functions in a positive way to assure the quality of products, rather than merely policing traffic in biologics. The aim is to further the application of the new materials to public health and medical practice, at the same time assuring conformance to the best standards for safety and potency applicable on the basis of current knowledge. Standards for safety are enforced by a system of periodic inspections of operations and records and the testing of products when necessary of all establishments that are licensed to sell or exchange biological products, including human blood for transfusion, across State lines.

2) Research on important problems relating to all aspects of production, distribution, use and effects of biological products, insofar as these are concerned with safety, purity and potency.

CONTROL

The basic instrument for the control of "biological products" provided in the Public Health Service Act is that of licensing. The legal requirement for licensing a biological product is that a license may be issued only upon a showing that standards designed to insure the continued safety, purity, and potency of the product have been met. Both the product and manufacturer are subject to licensing. Once an establishment has been licensed, it is inspected each year to determine continued compliance with standards. In addition, samples and test reports of each batch or lot of a product the manufacturer proposes to distribute are required to be submitted to the Division in the case of all but a few products where this is not deemed necessary for the assurance of safety, purity and potency. Test reports are checked; samples are tested when necessary. The lot in question is not distributed until a letter of authorization or release is issued by the Division.

During a recent 12-month period over 36,000 control tests were performed by Division personnel on the 3,559 lots submitted for release. This gives no idea of the total effort involved, however, since tests requiring a few minutes are given the same weight as those taking a month or more to complete.

The control activities of the Division require, also, the maintenance of a large number of different standard and reference materials. These are prepared in the Division or obtained by purchase. They are all tested in the Laboratories of DBS and distributed as needed. During fiscal 1966, over 7,000 such preparations were sent out to commercial establishments, health departments, universities and research organizations.

During 1966, thirty-four members of the scientific staff performed the required annual inspections. Sixty-five scheduled inspection trips were completed covering 236 licensed establishments, 103 locations, 134 blood donor centers as well as 10 applicants for an establishment license, for a total of 483 inspections.

INVESTIGATIONS

Investigations, in contrast with licensing and inspections, are conducted by the inspectors in the Office of the Director with assistance from laboratory staff when needed for peak loads. Inspections call for the expenditure of predictable periods of time on the part of the people involved and can thus be carried out with minimum dislocation of their other duties. Investigations, on the other hand, are essentially "open ended" with respect to time and must therefore be carried out by people who have this duty as their main function.

During 1966 the legal actions and investigations of possible violations of the Public Health Service Act involved a total of 243 man work days on travel status. One hundred and eighty man work days were devoted to consultations with state and federal officials, criminal trial preparation and participation, and witness interviews. The remaining 63 man work days on travel status were spent visiting both licensed and unlicensed establishments for enforcement purposes.

RESEARCH

The research activities of the Division cut across many disciplines and fields of interest. New and important techniques in immunochemistry must be exploited in relation to investigations of the induction of antibodies by vaccines, the measurement of various types of antibodies, the relation of the antibodies to protection against disease, and the relation of cellular mechanisms as well as antibodies to the entire immune mechanism. New techniques in virology have placed Division scientists in the forefront of knowledge in regard to viral oncogenesis and to means of measuring attentuation of virus strains for the preparation of vaccines.

Advances in virology are leading rapidly towards the development of new viral vaccines for mumps, para-influenza, rubella (German measles), respiratory syncytial virus, and many others. The unique features of each of these vaccines relative to the pathogenicity of the virus, the culture system, the techniques for assuring absence of adventitious agents, the inactivation techniques, the tests for safety, lack of communicability, and freedom from neurovirulence, etc. require the attention of expert staff.

DBS scientists, to be effective, keep constantly aware of research advances and design their own research activities so as to be prepared for control and testing problems which inevitably come before new or improved products can be entered into general use. Occasionally, because their own work towards these goals provides leads to products, DBS scientists produce an experimental immunogenic agent of their own. This happened recently in the course of work on rubella which was mentioned at last year's hearings. The scientists are continuing their investigative work on the experimental rubella vaccine and are making very desirable progress. This product has been distributed to interested researchers in the scientific community for additional study. It is hoped by all concerned that a safe, pure and potent vaccine will be available to the public within a reasonable time.

The same research team has recently developed a simple, rapid and inexpensive hemagglutination inhibition test for rubella antibodies. It is presently engaged in further perfecting this test, the widespread use of which could speed up work on rubella.

1967 AND 1968 PROGRAM PLANS

Within the last year the contracts program, stimulated by findings obtained within the last few years of the tumor-producing capabilities of various viruses, has been organized into a series of testing and research projects designed to answer problems of oncogenesis (the production of tumors) in relation to biological products. Work has already been initiated on tests of viral vaccines in the conventional test systems. Various studies are under way on methods for the detection of latent viruses in tissue culture cell preparations used for vaccine production, on adjuvant preparations purported to enhance immunogenicity of vaccines, and on chemicals added to inactivate viruses or to stabilize biologicals. Many of these, because of the inherent nature of the problems, are long-range projects which will require at least several years for their final results. Some

of these projects will require the production and use of newborn animals, which in the case of monkeys and dogs, will entail a considerable expenditure. Furthermore, in the analysis of cell chromosomes for example it will be necessary to exploit automated methods to the extent they are available, and possibly to invest in the development of additional graphic analysis techniques.

The initial expenditures of funds for this program were, of necessity, committed relatively late, because the conceptual development of a coordinated program of research and testing required a large percentage of the time and effort of Division staff. The program is gaining momentum, and there will be need for additional funds for additional projects and for confirmatory tests and tests of many new combinations of ingredients not included in the first protocols to obtain the precise information required. The "state of the art" in the entire field of viral and chemical oncogenesis is advancing so rapidly on many fronts that there is little doubt that new findings will require new investigations to assure the safety of biological products in these respects. In this budget, an additional $300,000 is requested to further the oncogenic program.

The Division has acquired additional facilities in 1967 and present space will be renovated in 1968; the budget contains no provision for additional funds or positions to expand the present staff. However, with expansion of physical facilities, the Division's scientists will have more desirable working conditions which will contribute to productivity. Of the $260,000 requested for equipment, $175,000 is required to equip renovated space in the present building and $85,000 is for specialized research equipment.

The 1968 total request is $60,000 less than the total obligations and balance in 1967. The unobligated balances resulting from the reserve in 1967 are $229,000, which, if removed from the base leaves a net increase requested for obligations only of $169,000. This net increase includes $560,000 for the expansion of programs as described above, $24,000 for mandatory items such as annualization of positions new in 1967 and annualization of the wage board pay increase, $184,000 for centrally furnished services from the National Institutes of Health Management Fund, offset by decreases of $7,000 for one day less of pay in 1968 and $592,000 for non-recurring items budgeted in 1967 to equip new facilities and renovate existing space.

FRIDAY, APRIL 7, 1967.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. KENNETH M. ENDICOTT, DIRECTOR, NATIONAL CANCER INSTITUTE

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ROBERT E. LEARMOUTH, EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE

DR. CARL G. BAKER, ASSOCIATE DIRECTOR FOR PROGRAM, NATIONAL CANCER INSTITUTE

EARLE L. BROWNING, BUDGET OFFICER, NATIONAL CANCER INSTITUTE

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. WILLIAM H. STEWART, SURGEON GENERAL

G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER

JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

(In thousands of dollars)

		1966 actual	1967 estimate	1968 estimate
	PUBLIC HEALTH SERVICE			
	Personnel compensation:			
11.1	Permanent positions	11,054	12,332	12,822
11.3	Positions other than permanent	73	75	75
11.5	Other personnel compensation	117	120	120
	Total personnel compensation	11,244	12,527	13,017
12.0	Personnel benefits	1,157	1,253	1,302
21.0	Travel and transportation of persons	476	535	550
22.0	Transportation of things	127	130	150
23.0	Rent, communications, and utilities	393	400	400
24.0	Printing and reproduction	316	450	450
25.1	Other services	2,652	2,800	3,000
	Project contracts	46,616	47,771	49,827
25.3	Payment to "National Institutes of Health management fund"	8,366	8,836	9,689
26.0	Supplies and materials	2,402	2,587	3,000
31.0	Equipment	1,388	1,400	2,000
41.0	Grants, subsidies, and contributions	82,798	92,788	98,993
	Subtotal	157,935	171,477	182,378
95.0	Quarters and subsistence charges	−15	−10	−10
	Total obligations: Public Health Service	157,920	171,467	182,368
	ALLOCATION TO VETERANS ADMINISTRATION			
	Personnel compensation:			
11.1	Permanent positions	557	617	618
11.3	Positions other than permanent	141	135	135
11.5	Other personnel compensation	2	1	1
	Total personnel compensation	700	753	754
12.0	Personnel benefits	50	57	57
21.0	Travel and transportation of persons	64	91	91
22.0	Transportation of things	1	2	2
23.0	Rent, communications, and utilities	1	1	1
25.1	Other services	5	6	6
26.0	Supplies and materials	29	31	31
31.0	Equipment	69	47	46
	Total, Veterans' Administration	919	988	988
99.0	Total obligations	158,839	172,455	183,356

Personnel summary

	1966 actual	1967 estimate	1968 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	1,336	1,421	1,461
Full-time equivalent of other positions	7	10	15
Average number of all employees	1,280	1,371	1,440
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466
ALLOCATION TO VETERANS' ADMINISTRATION			
Total number of permanent positions	76	82	82
Full-time equivalent of other positions	10	15	15
Average number of all employees	90	95	95
Average GS grade	5.5	5.5	5.5
Average GS salary	$6,278	$6,491	$6,548

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	68,884	77,550	83,317
(b) Fellowships	3,380	4,170	4,326
(c) Training	10,534	11,068	11,350
Total grants	82,798	92,788	98,993
2. Direct operations:			
(a) Laboratory and clinical research	13,823	14,776	16,065
(b) Collaborative research and development	52,535	59,815	62,985
(c) Biometry, epidemiology, and field studies	1,240	1,370	1,410
(d) Review and approval of grants	2,305	2,449	2,588
(e) Program direction	925	1,257	1,315
Total direct operations	70,828	79,667	84,363
Total program costs, funded [1]	153,626	172,455	183,356
Change in selected resources [2]	5,213		
10 Total obligations	158,839	172,455	183,356
Financing:			
16 Comparative transfers to other accounts	2,473	2,875	
25 Unobligated balance lapsing	2,394	313	
New obligational authority	163,706	175,643	183,356
New obligational authority:			
40 Appropriation	163,768	175,656	183,356
41 Transferred to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−55		
"Operating expenses, Public Buildings Service," General Services Administration (79 Stat. 531 and 80 Stat. 674)	−7	−13	
43 Appropriation (adjusted)	163,706	175,643	183,356
Relation of obligations to expenditures:			
10 Total obligations	158,839	172,455	183,356
70 Receipts and other offsets (items 11 to 17)	2,473	2,875	
71 Obligations affecting expenditures	161,312	175,330	183,356
72 Obligated balance, start of year	82,390	106,230	127,676
74 Obligated balance, end of year	−106,230	−127,676	−149,463
77 Adjustments in expired accounts	−3,617		
90 Expenditures	133,855	153,884	161,569

[1] Includes capital outlay as follows: 1966, $1,231,000; 1967, $1,447,000; 1968, $2,046,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $44,836,000; 1966, $50,049,000; 1967, $50,049,000; 1968, $50,049,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Name: Kenneth Milo Endicott, M.D.

Position: Assistant Surgeon General, Public Health Service Director, National Cancer Institute.

Birthplace and date: Canon City, Colorado, 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, 1958–1960.

Chief, Cancer Chemotherapy National Service Center, National Cancer Institute, 1955–1958.

Scientific Director, Division of Research Grants, National Institutes of Health, 1951–1955.

Chief, Section on Metabolic and Degenerative Diseases, Division of Pathology, National Institutes of Health, 1942–1951.

Medical Center for Federal Prisoners, Springfield, Missouri, 1942.

Maritime Quarantine Station, San Francisco, California, 1941–1942.
U.S. Public Health Service Relief and Quarantine Station, Portland, Oregon, 1940.
Commissioned in U.S. Public Health Service, 1940.

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."

Mr. NATCHER. The committee will come to order.

At this time we have before the committee Dr. Kenneth M. Endicott, Director of the National Cancer Institute.

Dr. Endicott, you are accompanied by several members of your staff that you will probably want to present to the committee at this time.

Dr. ENDICOTT. Yes, Mr. Chairman. I am accompanied by the executive officer of the Cancer Institute, Mr. Learmouth; the Associate Director, Dr. Baker, and our budget officer, Mr. Browning.

Mr. NATCHER. Dr. Endicott, I believe you have a statement you wish to present to the committee.

Dr. ENDICOTT. Yes.

Mr. NATCHER. You may proceed.

GENERAL STATEMENT

Dr. ENDICOTT. The National Cancer Institute is completing its 30th year in 1967. Major changes in cancer research have occurred during that time—changes that reflect the increased knowledge medical science has gained through intensive laboratory and clinical studies.

The need confronting researchers 30 years ago was to learn enough about the basic nature of cancer to attempt some practical solution to the problem. The emphasis had to be on basic studies of cell growth, biology and biochemistry, and experimental induction of cancer in animals. As knowledge of cancer grew, opportunities to undertake programed research aimed directly at control of cancer in man opened up, so that now research proceeds along both of these main approaches.

This change has not been sudden, but gradual. It has been a gradually evolving strategy of identifying problems in cancer causation and treatment and developing planned programs to solve these problems. Most of these efforts are related to many types of cancer.

I would like to amplify that a little bit. The search for cancer causes, generally speaking, does not deal with a specific kind of cancer. When one is studying cancer-causing effects of chemicals it is almost impossible to anticipate at the outset which part of the body may respond.

Similarly in the search for drugs with which to treat cancer, the animal model systems which we have for screening the drugs are not sufficiently predictive that we can tell in advance which kind of cancer, if

any, in man will be affected. So to this extent we have to deal with many types of disease lumped together and it makes the research rather difficult.

In recent years enough progress has been made in the case of a few types of cancer so it is possible to focus on a specific type of cancer. I would like to take this opportunity to review with you the progress of some of our more programed work now under way.

CANCER OF THE UTERUS

Our 1964 study showed continued improvement in survival for women with treated cancer of the uterus, mainly attributed to early detection of cancer of the neck of the womb by increased use of the Pap smear. This was shown to be a reliable casefinding test in large populations in a series of studies by the Institute in different parts of the country, notably in Memphis, Tenn., in cooperation with local health authorities and physicians.

In 25 years deaths from uterine cancer have been cut almost 50 percent in white women, and 40 percent in Negro women, in whom it occurs twice as frequently as in whites. We now have the knowledge to stop deaths from this form of cancer in the vast majority of cases. The barrier is no longer knowledge of how to do so, but getting women to take the test and providing technical and medical manpower to make the tests and follow through.

LUNG CANCER

Lung cancer is still the leading cause of cancer deaths in this country, particularly for men. There has been little improvement in the results of treatment, partly because only about 20 percent of lung cancers are discovered in a localized stage. Evidence from research led the Surgeon General's Advisory Committee on Smoking and Health to conclude in 1964 that cigarette smoking is causally related to lung cancer in men to a degree far outweighing all other factors, and that the data for women, though less extensive, point in the same direction. Later studies give further support to this conclusion. Scientists and physicians believe that if smoking were substantially reduced or discontinued, the result would be a marked reduction in pulmonary cancer, hence in deaths from this disease. Since smoking is such a deeply ingrained habit, effort is warranted to identify and eliminate whatever it is in tobacco or the smoking process that induces cancer. The National Cancer Institute and the Department of Agriculture are jointly trying to do this. Meanwhile, efforts are being made through educational campaigns to discourage smoking and to detect lung cancer earlier through periodic chest X-ray examination. We are on the search for more effective treatment for those stricken by the disease.

Incidentally, the cure rate overall is only about 5 percent, 5-year survival. The National Advisory Cancer Council has urged the creation of a lung cancer task force. The President has requested the Secretary to establish one and we are in the process of setting up a lung cancer task force to examine all possible avenues for bringing this emerging epidemic under control by one means or another.

LEUKEMIA

One of the most rewarding research approaches to specific types of cancer has been the study of leukemia, particularly acute leukemia in children. Drug treatment of this invariably fatal disase was begun 20 years ago by Dr. Sidney Farber at the Children's Cancer Research Foundation in Boston. The cancer chemotherapy program instituted in 1955 with its screening, pharmacology, and clinical trials activities, soon began to produce new drugs. The program brought together, in a cooperative effort to improve drug treatment, the resources of leading research institutions throughout the country, many of which were already supported out of the chemotherapy and grant programs. The National Cancer Institute's Acute Leukemia Task Force was established in 1962, and has been a most effective instrument for communication and the planning of action to be taken by investigators interested in the diverse aspects of this disease. As a result of these efforts, an increasing number of patients are surviving many months or years—some of them 5 years or longer—without evidence of disease.

This is in contrast to a survival of at the most 6 months before the advent of drug treatment. This gives greater hope than ever before that acute leukemia, and perhaps chronic leukemia, may one day be fully controlled. Part of this success can be attributed to new techniques for supplying leukemia patients the blood components needed to control hemorrhage and infection.

I would like to emphasize that it is necessary to use great caution in speaking of cancer cures because of the tendency of the disease to reappear after long intervals. It is my own growing conviction that we are probably curing some children with leukemia now, but it will be some years before one can say this with certainty.

Mr. SMITH. How many years?

Dr. ENDICOTT. I would think probably another 5 years before the investigators in the field will really feel confident enough to speak in this direction. It is really very spectacular to me.

I first became associated with the Cancer Institute only 10 years ago and actually set up the chemotherapy program. At that time the survival had been extended on an average from about 6 months to 18 months. Now there are a number of studies in progress in which 95 percent of the children go into remission. Many of them are in their third year of remission without disease.

I am almost certain that some of these children will survive and live a normal life.

Mr. HULL. Is there anything hereditary, a pattern in certain families?

Dr. ENDICOTT. There is some evidence to indicate that there may be some kind of genetic factor because the disease is especially prone to occur in certain types of congenital disease, such as Mongolism. The Mongolian idiot has a much higher risk of leukemia than the normal.

And there is an increased incidence, a very substantially increased incidence, of the disease in the case of identical twins. If one twin gets the disease, there is much greater risk that the identical twin will. But this may not be hereditary, it may simply represent something that occurs during the gestation period, and quite possibly could be due to a virus infection in the uterus.

I think the evidence is questionable on the genetic side.

Mr. NATCHER. During the past few months, Doctor, I have seen reports in the newspapers from time to time to the effect that in cases where mothers have been X-rayed a number of times before birth of a child, that in some instances leukemia has resulted. What about that, Doctor?

Dr. ENDICOTT. There have been several studies of population of women who for one reason or another were X-rayed during their pregnancy and the incidence of leukemia is increased, the risk of leukemia for the children they are carrying at the time is increased. This is quite consistent with observations of the Japanese populations that were exposed to the atomic bomb. In subsequent years they have an increased risk of leukemia and it is quite simple in the laboratory to produce leukemia in experimental animals with X-rays. So that this all hangs together.

In the case of experimental animal leukemia produced by radiation, there is evidence accumulating fairly rapidly which suggests that what really happens is that the X-ray activates a virus which is already there. So this may be an interaction of two factors really.

Through other studies we are attempting to find out whether a virus may be the causative agent in human leukemia, and if so, whether a vaccine can be developed against it. For the past 2 years the Congress has appropriated funds (over $16 million in 1967) for a special program of virus-leukemia research. This program is progressing according to plan and now includes some 70 projects for studies on the cause, prevention, and treatment of human leukemia, the possible relationship of animal leukemias to man, and the hazards involved in virus-cancer research.

As an aside, we were sufficiently concerned about the potential risk to the researchers of working with large quantities of cancer-causing viruses that we are building an emergency hazard facility in which to carry out this work. We expect it to be completed about the end of this calendar year, and I will sleep a lot more soundly at night when we do get into it.

Mr. NATCHER. You have a special report on the subject of leukemia that I think should be in the record.

(The report follows:)

SPECIAL REPORT: RESEARCH ON ACUTE LEUKEMIA AND RELATED DISEASES

More children aged 3–14 in the United States die of acute leukemia than any other diseases. Since 1947, however, biomedical research has produced striking improvements in life expectancy for victims of the disease. Twenty years ago a child lived about 3 months after diagnosis of his disease; today nearly 80 percent of those treated intensively live 2½ to 3 years. New drugs, new methods of using old drugs, and improved auxiliary therapy are continually improving the outlook for these patients.

Federal support is a major factor behind these favorable statistics. With the help of federal funds, 1,050 patients with acute leukemia (about half of all young Americans with the disease) were treated during 1966 at research centers participating in the National Cancer Institute program. Platelet transfusion programs, to extend life by preventing fatal hemorrhage, were introduced by the National Cancer Institute at 24 treatment centers during the year, increasing the number of such centers to 32. Relatively germfree facilities, to protect patients from serious infection during treatment, were supported at 5 centers. An allocation of more than $220,000 during fiscal year 1967 permitted leukemia patients from every State to travel with guardians to major treatment centers and be

housed nearby during outpatient periods. This innovation offered equal access to research facilities to all patients, despite their geographic location.

The remarkable improvements in survival are due largely to increasingly effective use of chemotherapy, often in high-dose combination schedules, wider use of platelet transfusions, and availability of new antibiotics to fight infections.

DRUG TREATMENT

One of the most effective treatment schedules for acute leukemia was reported by Dr. Edward S. Henderson and his colleagues of the National Cancer Institute at the May 1966 meeting of the American Association for Cancer Research. It consists of massive, intravenous doses of the drugs vincristine, prednisolone, 6-mercaptopurine, and methotrexate given intermittently for 15 months, with platelet transfusions and antibiotic therapy whenever indicated. Of 35 children with acute lymphocytic leukemia treated in this way, almost all were brought into complete remissions (disappearance of all signs of the disease) usually lasting about 13½ months. Most of the children who became ill again at the end of this period experienced a second remission after repetition of the treatment. As of November 1966, the anticipated survival time (life table median survival) projected for the entire group was three years, four months from the start of therapy, more than 13 times the life expectancy of children with actue leukemia 20 years ago.

Another promising approach to treatment of the disease was reported at the meeting by Institute grantee Dr. Phillip George and his associates at the St. Jude Children's Research Hospital of Memphis, Tennessee. These investigators used combination chemotherapy with five anti-leukemia drugs (vincristine, prednisone, methotrexate, 6-mercaptopurine, and cyclophosphamide) plus cobalt-60 radiation to the central nervous system. In November 1966 Dr. George reported to the Acute Leukemia Task Force that of the 32 children treated according to this system, almost all achieved complete remissions that lasted longer than 19 months. At that time the median survival time of these children was estimated to be about 28 months.

Another National Cancer Institute grantee, Dr. Isaac Djerassi, a member of the Acute Leukemia Task Force and a physician at the Children's Hospital of Philadelphia, Pa., recently reported encouraging results in the treatment of 15 children with acute lymphocytic leukemia. Using combinations of anticancer drugs, including infrequent but massive infusions of methotrexate, supplemented by platelet transfusions, Dr. Djerassi and his associates maintained all the children, without any deaths in the group, for periods ranging from 9 to 34 months at the time of his report.

The Acute Leukemia B Group of the Acute Leukemia Task Force has made favorable reports on the use of methotrexate, given into a vein twice a week, for successful maintenance of acute leukemia patients whose remissions has been induced by a combination of vincristine and prednisone. Among a group of 22 patients treated with this schedule, the median duration of this remission was one year, five months, and 18 of the 22 patients were still alive at the time of the report.

OVERCOMING THE PROBLEMS OF HEMORRHAGE AND INFECTION

By its destructive effects on bone marrow, acute leukemia interferes with a patient's ability to produce two important blood elements. These are platelets, which prevent hemorrhage or abnormal bleeding, and white blood cells, granulocytes, which help control bacterial infections. Ironically, the drugs used for treatment also damage the bone marrow and further increase the risk of fatal hemorrhage and infection. However, through the efforts of many scientists, and especially those on the Acute Leukemia Task Force, great advances have been made in reducing the threat of death from these causes.

Transfusions of blood platelets, sticky little disc-shaped particles, to replace the patient's missing platelets, have proved very effective in preventing or stopping hemorrhage in acute leukemia patients. Dr. Evan M. Hersh and his associates reported that at the National Cancer Institute, the rate of fatal hemorrhage dropped sharply from about 70 percent in the period 1954–1959 to 40 percent in 1960–1963. More recently it was observed that adequate transfusions of platelets could virtually eliminate acute leukemia deaths due to hemorrhage.

Platelets are relatively easy to obtain by plasmapheresis, a process in which platelets and plasma are removed from whole blood by centrifugation. Because

the blood donor's red cells are promptly returned to him, the normal donor may be able to give platelet donations as frequently as twice a week without ill effects.

The Acute Leukemia Task Force is working to extend this therapy to a greater number of acute leukemia patients. A $1.5 million appropriation from Congress during the present fiscal year is helping to make this lifesaving treatment available at a total of 32 leukemia centers.

The Acute Leukemia Task Force's subcommittee for training is updating a manual to assist medical personnel achieve the best results with platelet transfusions. The manual describes in detail methods of donor selection and recruitment, and the techniques of platelet preparation and administration. The subcommittee is also organizing training courses at the 6 leukemia center with the widest experience in platelet transfusions. Training will be offered to blood bank personnel and other key staff of centers joining the platelet transfusion program.

To assure a ready supply of platelets for transfusion, the Acute Leukemia Task Force has supported many studies of methods to freeze and store platelets, and much of the pioneering work was done by Drs. Djerassi, J. Cavins and Sidney Farber. Recently, Drs. Phin Cohen and Frank H. Gardner, National Heart Institute grantees at Harvard Medical School, reported a system for preserving platelet concentrates in glycerol, enabling freezing of the platelets which may be thawed later for administration to patients. The system is said to be one of the best yet devised. Platelets frozen by this and other methods are being sent to various medical centers for evaluation, following preliminary evidence suggesting that the frozen platelets will be therapeutically useful.

A reduction in fatal infections appears harder to achieve than control of hemorrhage, but there has been some progress. Fatal bacterial (staphylococcal) infections declined from about 25 percent in the years 1954–1959 to three percent during 1960–1963, but fatal fungal infections increased from 8.2 percent to 23.2 percent during the same period.

Newly developed antibiotics such as Kanamycin, Colistin and Cephalosporin have been of value in the struggle against infection. A search is under way for antibiotics more effective against gram-negative bacilli and fungi.

Granulocyte transfusions are being given with beneficial effects to some patients with bacterial infections at the National Cancer Institute, but it is difficult to obtain these cells in adequate amounts from normal, freshly drawn blood donations. Under a contract with International Business Machines, a centrifuge is being developed to separate granulocytes from the other blood elements which can then be returned to the donor. Encouraging progress toward this goal has been made during the past year.

Another infection-fighting approach is the development of relatively germfree treatment areas where patients may be hospitalized with greatly reduced danger of contracting infections. "Life Islands" or plastic isolators, which enclose a bed in a protective plastic bubble, are under study at the National Cancer Institute and four other major centers assisted by Institute funds. In addition, laminar-flow rooms are being developed in which a patient is safeguarded from infection by a circulating flow of virtually germfree air. The laminar-flow area gives the patient more room and has a better psychologic effect than the plastic isolator. If the patient is a child, a parent can be hospitalized with him. The laminar-flow concept is under study at three grant-supported treatment centers, as well as at the National Cancer Institute.

RESEARCH INTO CAUSES OF HUMAN LEUKEMIA

The strong possibility that a virus or viruses may be implicated in human leukemia, as they are in the leukemias of lower animals, is being investigated intensively in the Special Virus-Leukemia Program of the National Cancer Institute. This program, which seeks to identify a causative human virus and is tooling up for the development of a hypothetical human anti-leukemia vaccine, is described in a separate report to the Subcommittee.

In addition to viruses, several other factors appear to be implicated in the development of human leukemia. Some may predispose a person to the disease; another factor may trigger it. Dr. Robert W. Miller, Chief of the Epidemiology Branch of the National Cancer Institute, has reviewed these factors:

Chemical irritants.—Case reports of leukemia among Italian shoe workers strongly suggest that their disease was induced by prolonged exposure to benzene. There have also been reports of the incidence of leukemia following use

of certain drugs in other conditions, but the evidence for this is not conclusive. Studies are continuing.

Radiation.—A significant percentage of persons exposed to large doses of total-body irradiation, such as survivors of the atomic bombings in Japan and laboratory workers accidentally exposed to radiation, have been struck by leukemia. Even partial body irradiation, given as medical treatment of a spinal column disease known as ankylosing spondylitis, has been known to cause leukemia. Irradiation before birth such as an embryo may receive during diagnostic X-ray of a pregnant woman's abdomen, or even irradiation of the mother or father before conception occurs, may be involved in some cases of childhood leukemia. (Since the mid-1950's however, excessive use of medical X-ray has been curtailed, and National Cancer Institute epidemiologists Drs. Joseph F. Fraumeni and Miller recently noted a corresponding decline in leukemia mortality in the United States since 1961.)

Genetic factors.—Children with mongolism, a genetically determined disease, have 20 or more times the risk of developing leukemia than the rest of the population. Others with a high risk included in Dr. Miller's review are identical twins of children with leukemia and persons with the genetic diseases known as Bloom's syndrome and Fanconi's aplastic anemia. These patients, with high risk for leukemia, are being studied for clues as to the early preludes to the full blown disease.

Dr. Miller reported that there may be a common denominator in all the suspected factors in leukemia. The common factor may be an abnormality in cell chromosomes, the structures that pass hereditary information from one generation of cells to the next. Viruses, radiation, and certain chemicals are known to cause abnormalities in cell chromosomes, just as the genetic diseases are characterized by bizarre patterns of chromosome breakage and reunion or abnormalities in chromosome number.

The relationship of chromosomal abnormality to the development of leukemia is an area under extensive study at grantee institutions as well as at the National Cancer Institute itself, where chromosome studies are conducted on tissue from leukemia patients admitted to the research program of the National Institutes of Health.

CELL STUDY AN AID IN PLANNING THERAPY

Several relatively new concepts, derived from observations of leukemic cells in animals, are shaping current plans for human leukemia treatment.

The first is the concept that "100 percent kill" of leukemic cells is necessary to achieve cure. This concept was developed by National Cancer Institute staff members Drs. Emil Frei III and Emil J. Freireich, both now at the M. D. Anderson Hospital and Tumor Institute in Houston, and Dr. Howard Skipper, member of the Acute Leukemia Task Force, at the Southern Research Institute, Birmingham, Alabama.

They based their hypothesis on the observation made by Dr. Jacob Furth in 1937 that a single leukemic cell implanted in a mouse would multiply and eventually cause the death of the animal. Noting that the doubling time of the mouse leukemia L–1210 cell is about 12 hours, they determined that after 20 days the single cell would multiply to approximately 10^9 or 1,000,000,000 cells, sufficient to kill the mouse.

A second concept was 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 may cells are present. For example, the same drug dose will kill 99 percent of 100,000 leukemic cells or 99 percent of 100 cells, whichever number of leukemic cells is present in the animal. Moreover, if chemotherapy does not reduce the cell population at least 75 percent each day, multiplication of surviving cancer cells will outpace the inhibiting effect of the drug and will soon kill the animal. A variety of experiments have shown that the most effective chemotherapy is given as early as possible in the course of the disease, when leukemic cells are comparatively few, and consists of short, intensive courses of drug administration.

Efforts have been made to determine information for human leukemia similar to that cited for mouse leukemia. Estimates regarding the doubling time of human leukemic cells have ranged from three to six days, but a 4-day doubling time is now generally assumed. Autopsy studies by Drs. Frei and Louis B. Thomas at National Cancer Institute set the lethal number of human leukemic cells at 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. The first drug combination designed at National Cancer Institute

to meet these theoretical considerations and eradicate all leukemic cells was the 4-drug VAMP treatment (*V*incristine, *A*methopterin, 6-*M*ercaptopurine, and *P*rednisone). In this study the median duration of remission, unmaintained by drugs was in excess of 160 days, suggesting that relatively few leukemic cells remained at the end of treatment and that the patients were almost, but not quite, cured.

Two patients treated in this VAMP program remained in complete remission for more than three years. However, one of them recently relapsed with Burkitt's lymphoma, a disease which seems to be related to acute leukemia. Burkitt's lymphoma is discussed below in greater detail.

The study reported by Dr. Henderson, mentioned above, was a more recent effort to utilize the "100 percent kill" concept. Most of the patients in this study were in complete remission well past the theoretically critical period (160 to 170 days) required for total kill of leukemic cells. Hence the possibility must be considered that subsequent return of the disease was due to re-induction by a virus or some other causative agent.

Intensive laboratory studies of cells are continuing under National Cancer Institute auspices in an effort to develop more effective ways of interfering with cell growth by drugs. There has been convincing evidence that alterations in the size of the dose and frequency of administration can markedly influence drug effectiveness, and that drug "pulses" can be timed to damage cancer cells irreparably but allow normal cells (with their longer "resting" phase in the cell growth cycle) to recover from drug damage.

National Cancer Institute scientists are attempting to measure accurately the major active periods in a cell's life cycle, namely: G–1, the first growth period; S phase, the period in which DNA is synthesized; G–2, the second growth period; and lastly mitosis (M), when the cell splits into two daughter cells. Recently a member of the Cell Kinetics Group of the Acute Leukemia Task Force, Dr. W. R. Bruce and his associates at the University of Toronto reported at the Ninth Canadian Cancer Congress that some anticancer drugs kill cells only in one phase of the cell cycle. For instance, vinblastine and methotrexate kill cells only in the S phase. Others, such as 5-fluorouracil, kill active cells in all phases of the cycle much more efficiently than they kill cells at rest. A third class of drugs kills cells actively in cycle or in a resting, nondividing stage. Both the cycle-specific and the phase-specific drugs produce their anticancer effects by virtue of the large differences in the doubling time of cancerous and normal cells, and it is these drugs with which physicians hope to achieve greater selective toxicity against leukemic cells.

Further studies are under way to plan administration of combinations of drugs carefully timed to capitalize on vulnerable periods in the life span of leukemic cells. Hopefully, a cumulative effect will be 100 percent kill of leukemic cells, with relatively little effect upon normal cells.

BURKITT'S LYMPHOMA

Since the publication in 1958 of a paper entitled "Sarcoma Involving Jaws in African Children" by British surgeon Denis Burkitt, there has been great interest in medical circles regarding this most common cancer of African children. Now called Burkitt's lymphoma, the cancer most frequently affects the jaw, bony socket of the eye, or organs in the abdomen. It grows rapidly and, if untreated, usually causes death within 12 months.

Although a few cases have been reported in the U.S. and Europe, Burkitt's lymphoma is chiefly associated with a geographic belt extending across central Africa from east to west. The disease occurs almost exclusively at elevations below 5,000 feet and at temperatures above 60° F., in regions where the annual rainfall is greater than 20 inches. This low, humid area is the habitat of the Anopheles and Mansonia mosquitoes.

Noting the rarity of acute leukemia among African children, scientists have speculated that acute leukemia and Burkitt's lymphoma may share a common cause and that the disease may express itself in different forms according to the environment. They suggest that the situation may parallel one found among experimental animals, namely the induction of disease in mice by the Gross virus, which causes either leukemia or lymphoma depending upon experimental conditions. Although viruses have not yet been found to cause either human acute leukemia or Burkitt's lymphoma, a search for causative viruses is under way.

A virus similar to the common herpes or cold sore virus has been found in many tissue culture lines of Burkitt's lymphoma cells, not only those originating in

African children but in American children as well. In addition, a virus called Reovirus 3 (*R*espiratory, *E*nteric, *O*rphan) that is found in human lungs and intestines has been detected in various Burkitt's lymphoma cases. Antibodies to Reovirus 3 have been reported in most of the lymphoma patients studied, but in only a few controls. Whether either or both of these viruses plays a causative role in the development of the disease has not yet been established. In addition to virus infections, malarial infections are common in central Africa, and it has been suggested that they may alter the patient's immune response and interfere with his ability to reject Burkitt's lymphoma.

Up to the present time, Burkitt's lymphoma has been treated chiefly by chemotherapy since radiation facilities are unavailable in Africa. Surgery has proved to be an unsatisfactory method of treating the disease. More and more reliance is being placed on drug therapy, with some very encouraging results.

Cyclophosphamide has been found effective in treating all stages of the disease. Methotrexate, given in large doses, is useful only in the early phases. Other drugs, such as melphalan, ortho melphalan and vincristine, have some activity against the disease.

Of 181 cases reported by Burkitt, Ngu and Clifford, 25 patients no longer under treatment are free from all evidence of the disease for periods ranging from 6 months to 6 years. In addition, a significant number of the 181 patients were lost to follow-up, and it is believed that many of them failed to return for treatment because their disease did not recur.

The implications of Burkitt's lymphoma for the treatment of acute leukemia were discussed in January 1966 at a meeting in Kampala, Uganda convened by the Chemotherapy Panel of the International Union Against Cancer. Two general approaches were suggested: (1) use of drugs in large single doses or short courses when a patient's disease is in complete remission; (2) bolstering of a patient's immune response by immunization techniques while he is in complete remission and not receiving any drug therapy. The participants at the meeting were in general agreement that long survivals were probably induced by a combination of chemotherapy and the patient's own defense mechanisms.

A more intensive study of Burkitt's lymphoma is planned by National Cancer Institute staff in cooperation with scientists in Africa investigating the disease, commencing with another meeting in Nairobi in January 1967.

It is believed that information gained in the treatment of Burkitt's lymphoma will be of value in improving the treatment of acute leukemia.

A LOOK AT THE RECORD

1967 marks the 20th anniversary of the first advance in the treatment of acute leukemia. In November 1947 Dr. Sidney Farber and his associates at the Children's Cancer Research Foundation in Boston were able to induce temporary remissions in 10 of 16 children with acute leukemia, the first such remissions ever achieved by any form of therapy. The remissions were induced by a drug called aminopterin, long since replaced by new and more effective drugs.

An indication of the gains made since 1947 can be discerned from the results of treatment described earlier in this report. Another criterion is the number of known long-term survivors, patients living five years or longer after diagnosis of their disease. Dr. Joseph Burchenal, a member of the Acute Leukemia Task Force and associate medical director of the Memorial Sloan-Kettering Cancer Center, reported that the Task Force's worldwide registry of long-term survivors now includes 140 persons, most of whom are children.

In Novemhber 1966 Dr. Burchenal reported that 27 adults and 75 children were in good health, with no evidence of disease, 5 to 16 years following diagnosis. (The remainder, 15 adults and 38 children, are either alive with some evidence of disease or have since died.) Data are incomplete as to the number of the patients still receiving treatment. However, 22 long-term survivors are known to be free of disease without any treatment for periods ranging from 3 to 14 years. These long-term survivors are being studied to discover any similar factors in their life histories or treatments that might lead to successful treatment of others. This study is just one of dozens of National Cancer Institute supported studies under way in an effort to bring curative treatment to all victims of the disease.

The Acute Leukemia Task Force, under the direction of the National Cancer Institute's Scientific Director for Chemotherapy, Dr. C. Gordon Zubrod, is unsparing in its efforts to eradicate the leading fatal disease of children in the United States. The Task Force's goal is one of the most difficult that medical

science faces. Its program is as ambitious as any sponsored by the U.S. Government. Scientists are convinced that a means will soon be found to control this cruel killer of children.

CANCER OF THE LIVER

There are toxic products of fungi that contaminate food and may be implicated in cancer of the liver in Africa and cancer of the stomach in Japan. Among them are products of the mold *Aspergillus flavus* called aflatoxins. Aflatoxins in feed were found to be the primary cause of an epidemic of liver cancer in hatchery-raised trout in this country a few years ago. Since then, four major aflatoxins have been shown to produce liver cancer in mammals, birds, and fish. We have consequently become greatly interested in the possibility that aflatoxins may have a role in causing cancer in man—a possibility supported by statistical data showing patterns of cancer incidence in other countries. We have therefore stimulated analytical, biological, and biochemical studies of aflatoxins and other mycotoxins to evaluate their toxicity and cancer-causing potentiality. This is one kind of environmental approach to cancer prevention and control to which a large share of our research effort is given.

I think it would be appropriate to state for the record that this problem of mycotoxins, the aflatoxin being the first of the series, is likely to have a major impact on food technology in this country. These molds grow in foods which are stored before they are properly dried. It is especially prone to occur, for example, in the storage of peanuts. It also occurs in the storage of some of the protein concentrates like cottonseed meal or linseed meal.

The molds are widespread in nature and in stored grains and in many different types of food, molds grow and are capable of producing these toxic materials.

I think before we are all finished we are going to end up seeing some major changes in the way that the food is harvested and stored in order to prevent formation of these poisons in the food.

This is a new development, it has all happened within the last 5 years, and it is going to cause us a lot of trouble, not only in other parts of the world, but also in the United States.

RESEARCH USING OCCUPATIONAL GROUPS

There are also important opportunities for research using occupational groups as prime populations in which to study such fundamental questions as why all persons exposed to a cancer hazard do not develop the disease, and what are the earliest states of tissue reaction that may progress to overt disease. Enzyme and other protein studies may identify metabolic abnormalities in organs affected by cancer-causing agents, and such studies may open up opportunities for prevention of the disease.

It is not well appreciated, I think, that a substantial but unknown amount of cancer is being prevented all the time by safety measures in industry and in occupations; once the presence of a carcinogenesis chemical in an industrial process is established, it is usually possible either to find an alternative substance or, if that is not possible, to engineer the industrial process in such a way as to prevent human contact with the chemical.

These discoveries occur constantly and the chemicals are quietly engineered out of the environment and if they were not we would be in a lot more trouble than we are today.

Attempts such as these to get at the problem of cancer in man take off from points of departure that occur from time to time with the steady advancement of research on all aspects of the cancer problem. The emphasis on fundamental research in the early years of the Institute's history gradually permitted the delineation of areas offering special promise for investigation. One of the first was drug treatment, and the chemotherapy program was launched in 1955.

Another was "carcinogenesis"—the doctor's term for cancer-causing. I am sorry it slipped in there—and for the past several years we have been expanding laboratory work and statistical and epidemiological work to learn how environmental factors cause cancer and how they may be controlled.

ESTABLISHMENT OF DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

I would like to mention something which has happened this year which I regard as being of great importance in the field of carcinogenesis, and that is the establishment of a new Division of Environmental Health Sciences, with which we expect to work very closely and are already jointly planning programs. The only bad part of it is that Dr. Shannon took my right-hand man, Dr. Kotin, to head it up and we are going to miss him very much.

As I have already mentioned we have more recently organized the many-faceted special virus-leukemia research program.

We have found the task force technique to be very effective for reliable delineation of new areas for programmed research. The acute leukemia task force was so successful as a communication service that the techniques of this group have been freely applied to others. In 1964 we organized the chronic leukemia-myeloma task force with the object of controlling chronic leukemias and plasma cell myeloma with drugs. In 1965 we established the lymphoma task force to correlate research on drug and radiation treatment of Hodgkin's disease and other malignant lymphomas. A solid tumor task force was organized in June 1966 to intensify studies of the treatment of these cancer forms.

BREAST CANCER IN WOMEN

One of the most challenging problems is breast cancer in women, on which little progress has been made for the past 30 years, at least as measured in terms of mortality.

The Congress was therefore fully justified in approving a line item appropriation for a breast cancer task force which was established in April 1966. This group has formed subcommittees to work on the problem of identification of the high-risk (short-survival) patient, and to set up a national study of extensive versus limited surgery for localized disease.

The task force is also reviewing the animal screening data of the Cancer Chemotherapy National Service Center to make recommendations about the best animal tumors for the prediction of hormone and other drug treatment of breast cancer. It is beginning to intensify the efforts in the field of viral causation of breast cancer.

The evidence here in man is not as good as it is in the case of leukemia, but in the experimental animal, virus plays an important role in the causation of breast cancer. It usually requires also some genetic factor and is dependent upon the presence of functioning ovaries in the female animal. So this is a possibility at least, but the work is not so far along.

CHORIOCARCINOMA TASK FORCE

We are presently developing a choriocarcinoma task force as a transitional step toward a new way of using these groups to translate research results obtained from the laboratories and clinics directly into nationwide projects for the control of specific malignant diseases.

Dr. Shannon referred to this in his testimony yesterday and I would like to amplify my remarks a bit in this area.

Some few years ago Dr. Roy Hertz, working in the National Cancer Institute, succeeded in causing remissions of choriocarcinoma in very advanced cases. This is a cancer which is derived from the placenta and occurs as a result of pregnancy. It grows rapidly and spreads quickly, especially to the lungs, and is a rapidly fatal disease. Using a drug which was already known to be effective in acute leukemia, Dr. Hertz gave very intensive treatment with this drug Methotrexate and succeeded in producing a remission in the disease in the advanced state. As work progressed, he became sufficiently confident of the effectiveness of this treatment to use the drug treatment early in the disease instead of surgically removing the uterus.

This was an important step forward because the women affected are in the childbearing age and many of them still want more children. As he gained confidence and began using the drug earlier in the disease, it became apparent that the drug actually could control the disease and cure it without the use of surgery. The treatment is dangerous, it must be followed very closely in the laboratory.

The tumor produces a hormone which, with very careful measurements, can be detected and you can tell when you have destroyed the tumor because you can find no more of the hormone.

So about a year ago Dr. Hertz approached me and suggested we try to set up a program which would try to wipe out choriocarcinoma as a cause of death in the United States. It is a relatively rare disease. There are very few investigators competent to do the hormone assays and to do the therapy, but because the disease is relatively rare we believe that 8 to 10 centers in the country where both the tests and the treatment can be given will be sufficient to meet the needs, and we are in the process of establishing these centers in collaboration with the cancer control program of the National Center for Chronic Disease Control. They are going to finance the laboratories and we are going to finance the experimental therapy.

This disease is much more common in other countries, notably in Asia, and I feel if we are successful here with this model system that this might make an excellent export perhaps through AID programs or something of the sort to other countries where it is a very important cause of death.

PROGRESS AGAINST CANCER

Although we are directing programed research in areas of special promise and need for target type investigation, we are not unmindful

of the serious threat posed by the cancer problem as a whole. The situation is one of paradox. During the 30 years that the Federal Government has fostered cancer research through National Cancer Institute programs, the death rate from cancer has gone up from 112.5 to 153 per 100,000 population. On the other hand, we are curing more cancer today than 30 years ago. Around 1937 the ratio of patients who survived 5 years increased from fewer than 1 in 5 to 1 in 4. Now, the ratio is 1 in 3, and under optimum use of present-day methods of early diagnosis and treatment it could be further improved to 1 in 2. However, we are losing ground so long as the cancer rate continues to go up—and it is still going up. While lung cancer accounts for much of the increase, other forms of cancer are also occurring with greater frequency while a few, such as stomach cancer, are decreasing.

There is still a great deal to be learned about the nature of cancer and how to deal with it as a disease in man. Thirty years ago staff scientists and grantees of the National Cancer Institute concentrated their research on the cell, trying to find out how a normal cell becomes cancerous and produces more cancer cells. We still haven't found out. Although research has since ranged over much wider fields, the ultimate solution to the cancer problem is probably still locked in the cell. We believe, however, that efforts to control cancer in man need not—in fact, cannot—wait for that final solution to come. Time and time again, we have seen how knowledge gained from diversified research can be fitted together and used as a point of departure into important new areas that invite exploitation by the problem-solving approach.

In its first public report entitled "Progress Against Cancer," issued last December, the National Advisory Cancer Council stated that the only avenue to the solution of the cancer problem; namely, research, is basically more sound today than ever before. It said that the opportunity to get on with the final solution to the complex problem of cancer has never been more promising. I am in complete agreement with the council's comments, for I share their confidence in the ability of medical science to bring cancer under control as it has brought many other diseases under control. Cancer is a stubborn problem, but cancer researchers are stubborn people in dealing with it. Something has to give way, and cancer is giving way already, however slowly.

Mr. Chairman, the request for the National Cancer Institute for 1968 is $183,356,000, compared to the 1967 operating level of $172,455,000. The 1968 budget request contains increases of $10,901,000 including: $5,767,000 for research grants; $156,000 for research fellowships, $282,000 for training grants; $1,289,000 for direct research in our general laboratories and clinics; $3,170,000 for collaborative research and development; $40,000 for biometry, epidemology, and field studies; $139,000 for review and approval of grants; and $58,000 for program direction.

SUMMARY OF BUDGET REQUEST

Mr. NATCHER. Dr. Endicott, we want to thank you for your statement.

The adjusted appropriation for 1967 is $172,768,000 and the request for 1968 is $183,356,000, for an increase of $10,588,000. Is that correct?

Dr. ENDICOTT. Yes, sir.

BUDGETARY RESERVE FOR SAVINGS

Mr. NATCHER. Before we discuss the figures and go into details, tell us what adjustments you have made in order to come up with this "Unobligated balance, reserve" of $313,000 out of this year's appropriation. Explain that to the committee, please.

Mr. LEARMOUTH. The $313,000 that was placed in reserve was met primarily by delaying hiring of personnel that were to come on board and through savings resulting from delays in funds becoming available. It was possible to make these savings without serious damage to the program.

Mr. NATCHER. Doctor, could we assume that this reserve would indicate that you could use the same amount that you had in fiscal year 1967?

Dr. ENDICOTT. For the coming year?

Mr. NATCHER. Yes.

Dr. ENDICOTT. Yes; there is no question about that.

Mr. NATCHER. You could use that and you would not need any more. In view of the fact that you could get along with less than the amount appropriated for 1967 do you really need this increase, Doctor?

Dr. ENDICOTT. Yes, sir; we certainly do. We need it very badly.

Mr. CARDWELL. Could I comment?

Mr. NATCHER. Yes.

Mr. CARDWELL. This is another one of the items we have discussed several times thus far in our hearing. It was an action taken by the Department involving not only the National Cancer Institute, but other programs, and was a part of the HEW contribution to the President's effort to restrict outlays during 1967. It did in effect slow down the rate at which the National Cancer Institute might have awarded new cancer grants, and it does indirectly have a program effect. If we are denied these funds in 1968 we would in effect be cutting back the program by this amount.

PERCENTAGE OF INCREASE REQUESTED

Mr. NATCHER. Doctor, your increase is less than the average for NIH, I believe just a little under 6 percent. This probably would not cover the increased costs, will it?

Dr. ENDICOTT. In general, no. I think perhaps our lower percentage of increase ought to be viewed with the realization that a substantial part of our program is a contract program in which we design the work to be done and go get somebody to do it. This is a different situation than the one Dr. Shannon was speaking of so feelingly yesterday in the academic institutions in which there is a constant stream of promising young men coming out of the training programs ready to enter the working pool. These contract programs are carried out mostly within an industrial framework and these are programs which can be held level in times of budget stress without the same impact that you have in the grant area.

COST OF MOVE TO NEW BUILDINGS

Mr. NATCHER. In addition to the usual cost increases, you will have costs such as setting up laboratories when you move into the new building. How much will the cost of this move total?

Can you give the committee some idea about this matter?

Dr. ENDICOTT. There are identified items which I can supply for the record totaling about $700,000, but this does not completely reflect the cost because we have been accumulating some equipment for the past several years in anticipation of getting into these buildings and will be buying some out of operating expenses which are not specifically earmarked.

We will probably not complete the occupation of these buildings in this next fiscal year. Just a guess, I would say probably something on the order of a million to a million and a quarter.

INDIRECT COST ANALYSIS

Mr. NATCHER. You show a transfer of $112,000 to the Office of the Secretary for indirect costs analysis. What does this mean, Doctor?

Dr. ENDICOTT. This refers to the establishment of institutional indirect cost rates, which is carried out in the Office of the Secretary for the various programs.

CHEMOTHERAPY OF SOLID TUMORS

Mr. NATCHER. Just how much have you done in research in the past on chemotherapy of solid tumors?

Dr. ENDICOTT. We have done a lot of work on chemotherapy of solid tumors.

Mr. NATCHER. I had the understanding that you have not done very much as far as chemotherapy of solid tumors is concerned. I believe in the report last year the committee indicated its desire that you do more along this line and asked you to prepare a long-range plan.

Just what have you done, Dr. Endicott?

Dr. ENDICOTT. Perhaps I might give a little background here.

In screening for cancer drugs, we examine many natural products and synthetic chemicals in animal tumors. One cannot tell what kind of cancer in man may be affected by these drugs until he tries. So it has been a regular part of our program from the very beginning when we find a promising drug in the laboratory to test it against all forms of cancer. There has been some misunderstanding, I think, with the regard to lack of effort.

It has not been lack of effort with the solid tumors, it has been lack of success.

There has been some progress. One milepost occurred a few years ago as a result of some work by Dr. Curreri at the University of Wisconsin. He discovered a new drug called 5-fluorouracil. This was the first drug that had much activity against tumors of the intestinal tract. Subsequent work has been sufficiently encouraging that I have just appointed a task force on cancer of the colon and rectum to really attack this problem in an all-out way, not only from therapy but also from a diagnostic standpoint.

There is I think good reason to believe that an effective early use of drugs combined with therapy can very substantially increase the cure rate of cancer of the colon and rectum.

I have already mentioned the breast cancer task force. Here the lead is not so much in therapy as it is that we believe we are about to establish a system of hormone analysis which will make it possible

for us to predict the probable course of the disease in the individual woman, so that in appropriate cases we can use very aggresive therapy at the time of surgery, which will greatly increase the cure rate. This is a very disfiguring operation and if this is coupled with radiation and chemotherapy, it is really a pretty severe treatment. If we could sort out those cases that will do well with conservative therapy, perhaps just simple removal of the breast from those that are not going to do well, and concentrate our intensive therapy there, I think we may get some real mileage for the first time in the breast area.

I mentioned lung cancer, this is a solid tumor, and we have set up a task force also under the chairmanship of Dr. Rubin Flocks, in Iowa, to study cancer of the prostate and bladder. This is another area in which I think we have some workable leads.

It has been a disappointment of course that our drugs have not been effective in some of the most common forms of cancer.

Mr. NOTCHER. I see you have a special report on this subject. Without objection, we will place that in the record.

(The special report follows:)

SPECIAL REPORT: CHEMOTHERAPY OF SOLID TUMORS

During the past 20 years major advances have been made in the control of cancer by chemotherapy or drug treatment. Achievements have been primarily against cancers whose cells multiply rapidly, such as the leukemias, lymphomas, choriocarcinoma, and to a lesser extent, cancer of the testes and childhood solid tumors. Cell division rates and other growth characteristics of these cancer types have been examined and the findings have helped scientists design more effective schedules for administering drugs. In addition, two animal tumors have been found to serve as a reliable screen for testing drugs against fast-growing cancers, so that drugs found active in these animal systems can be selected for the clinic with a good possibility of usefulness.

By contrast, the most common solid tumors, such as cancer of the colon-rectum, breast, and lung, are slow-growing tumors. Facts known about the cell division cycles of fast-dividing cancer cells are of uncertain value in planning drug treatment of these slow-growing cancer types. Although known to be long, the cell growth cycles of individual solid tumor types are not well established. There is particular need for better information on the period of DNA synthesis and other cell cycle events, by various cell types, to determine the time of the cancer cell's greatest susceptibility to drug effects. Better research methods for studying these cell cycles in patients with solid tumors must be developed.

Two animal tumors, the L–1210 mouse leukemia and the W–256 intramuscular rat tumor, which are characterized by rapid cell division, select all but one of the agents active against certain human solid tumors, which are characterized by slow cell division. The drugs selected, however, have modest inhibitory effects on the slow-dividers, but these effects are not complete or prolonged.

Without the basic cell information needed to plan effective drug therapy, or assurance that the available drug-detecting animal systems are useful for human solid tumors, cancer scientists have been severely hampered in their effort to treat advanced cancers of the solid-tumor type.

FORMATION OF A SOLID TUMOR TASK FORCE

An organizational move toward solving these and other problems was made in June 1966 when the National Cancer Institute established a Solid Tumor Task Force. The National Cancer Institute used techniques learned in leukemia research to develop the new task force, and mobilized leading members of the biomedical community for the effort. The membership includes representatives of the nationwide cooperative groups experienced in solid tumor treatment, namely the Central-Western Clinical Drug Evaluation Program, Eastern Solid Tumor Group, Southwest Group, Western Solid Tumor Group, Southeastern Group, the five cooperative groups of the Veterans Administration hospitals, and

spokesmen for the Acute Leukemia B Group and Children's Cancer Group A. Interested independent investigators are invited to attend, and an effort is made to include surgeons and internists to allow the group to consider their differing approaches to the therapy of solid tumors.

As one of its first actions, the Solid Tumor Task Force established a committee of scientists highly experienced in planning the design and conduct of clinical studies to serve as an advisory panel to the cooperative groups. This committee will review the present systems for evaluating drugs in patients with solid tumors, and advise on ways in which to find more effective dose schedules.

Like other NCI Task Forces, the new Solid Tumor Task Force is benefiting from the basic work of the Clinical Trials Group, a "core" group of chairmen of cooperative chemotherapy study groups and a few independent investigators. This group carefully weighs screening, toxicologic and pharmacologic data in order to select the most promising drugs for initial clinical trials. Chemical agents selected by this group for clinical trial are made available to the cooperative groups and their representatives on the Solid Tumor Task Force.

The new task force will seek to uncover and analyze data on solid tumor cell growth cycles, to discover an animal screening system that will reliably predict drugs useful in human solid tumors, and will attempt to define criteria for measuring drug effectiveness against solid tumors.

From the start of the new group, its members were aware that there would be over-lapping in some of the data under study by this group and the several disease-oriented task forces already devoted to the study of the individual solid tumors:

The Brain Tumor Task Force, a group of neurosurgeons active in the chemotherapy of brain tumors, who pool their clinical research effort in a collaborative program under the auspices of NCI and NINDB.

The Breast Cancer Task Force, a group especially funded by Congress to evaluate hormonal, surgical, radiologic and chemical approaches to treating breast cancer, and to investigate the possibility of a viral cause.

The Choriocarcinoma Task Force, a group concentrating on national control of this rare uterine cancer by application of the chemotherapy regimen developed at NCI by Drs. Roy Hertz, Min Chiu Li, and their associates.

Intensive Study Groups, newly formed, share the same broad interests as the Solid Tumor Task Force concerning treatment and, in addition, probe more deeply into causative factors and the natural history of the disease in those sites.

NEW MEASUREMENTS OF DRUG EFFICACY

In the months just past, some progress has been made on one of the basic problems confronting the Solid Tumor Task Force, reliable measurement of drug effectiveness. One of NCI's major collaborators and contractors, the Southern Research Institute (SRI), conducted experiments in animal tumor chemotherapy that may indicate a need for new criteria to judge drug effectiveness against solid tumors. The time-honored measurement, reduction in tumor mass, may not give a satisfactory evaluation since dying and dead tumor cells occupy volume and comprise mass. The break-up and disappearance of the drug-killed cells is a slow process. Hence a judgment of drug effect based solely on changes in tumor size may underestimate the capacity of the drug.

SRI's experiments with a cancer of the hamster, the Fortner "solid" plasmacytoma, treated with the drug cyclophosphamide indicate that the affected cancer cells are killed within an hour after the drug is injected, yet measurable tumor shrinkage occurs only over a 1- to 2-week period. Repopulation by surviving cancer cells begins long before the treated tumor has been reduced to smallest size. Thus the best time to administer a second course of treatment (if it can be tolerated by the host) may be much earlier than the time when the tumor has shrunk to its smallest dimensions.

These NCI-supported studies further suggest that a better estimate of solid tumor cells killed by a given drug may be derived from the life span of plasmacytoma-bearing hamsters treated with the drug. Hence this cancer in the hamster may provide a basis for establishing drug dose levels and schedules directed to the goal of 100 per cent kill of solid tumor cells.

ARE THE KNOWN DRUGS ADEQUATE?

Twenty years of intensive search for chemotherapeutic agents has yielded more than 2 dozen compounds effective in various forms of cancer. However,

some forms of cancer, such as those of the stomach and bladder, are virtually unresponsive to any form of drug therapy, and the major forms of solid tumors respond only slightly to drugs. The drugs presently known represent 15 basic molecular structures. Entirely new chemicals may be needed to exert therapeutic effects on the unresponsive solid tumors.

To guide NCI chemotherapists in planning the kinds of compounds to be prepared for use against solid tumors, the Scientific Director for Chemotherapy, NCI has formed a Structure: Activity Advisory Group consisting of leading American organic chemists. The structure and activity of each of the known drugs are being reviewed by this group and their clinical usefulness analyzed to determine the most promising areas for future drug development.

On the other hand, the known drugs and their effect on solid tumors have been inadequately explored to date, particularly by the pharmacologists. It is quite possible that a unique dose level, schedule, and route of administration of an already known drug or drugs might produce the necessary therapeutic effects. It is of vital importance that all of these factors be explored for the reason that it is essential to establish for each major tumor type certain drug treatment factors necessary to kill tumor cells: 1) the amount of the drug needed to reach tumor cells and 2) the length of time the drug should remain in contact with the tumor cells. Further information on the length of time for a cell to reproduce would indicate the optimum frequency of the treatment, that is, the interval between "pulses" of drug administration in which normal cells recover from the drug but cancer cells do not.

Other evidence that the known drugs have been inadequately evaluated continues to emerge. A recent study of the drug cyclophosphamide at the Southern Research Institute suggests that this useful anti-cancer compound may split into several fractions, only some of which have anti-cancer activity. Further studies of metabolic changes in this and other familiar drugs may lead to discovery of new ways of using them more effectively and without the hazards of high dose or cumulative toxicity. The National Cancer Institute is expanding its pharmacologic studies in order to use active drugs at maximum efficiency.

CONTINUING CLINICAL STUDIES

While concepts are being evaluated and working groups are tackling organizational as well as basic research problems, the day-to-day treatment of advanced cancer patients continues according to approved protocols. Within recent months several interesting, mostly preliminary reports of cancer drug effectiveness have been under study by the NCI Chemotherapy Group. They concern the clinical evaluation of drugs in various forms of solid tumors which, in advanced stages, do not respond to surgery or radiotherapy. A few of these findings follow.

Cancer of the testis is the most common malignant tumor of males between the ages of 29 and 34. Some types of the disease, often unresponsive to surgery and radiotherapy, are now found to benefit from drug treatment.

Three forms of this cancer are responding to combination chemotherapy with the drugs Actinomycin D, methotrexate and chlorambucil. Dr. David A. Karnofsky, member of the Clinical Trials Task Force, reported to task force members that among 150 patients with advanced testicular cancer treated with these drugs at the Memorial Sloan-Kettering Cancer Center, 11 achieved remissions. The survival time of these patients ranged between 1 and 10 years, with 5 patients surviving free of disease beyond the 10-year point.

In another unpublished study, Dr. Theodore Medrek, also on the Clinical Trials Task Force, reported 165 cases of testicular cancer treated with Mithramycin, an antibiotic produced through the NCI program, under a contract with Charles Pfizer and Company, Inc. Seventeen patients, mostly with embryonal cell carcinoma, experienced complete remissions of 6 months to 6 years, and 47 had partial remissions.

Glioblastoma, an invariably fatal brain tumor, has not yet proved responsive to treatment by any form of chemotherapy. However, preliminary reports on the administration of Mithramycin have been encouraging; Dr. Medrek reported that 10 fair-to-good partial remissions were observed.

Because of the variable course of the disease, the Brain Tumor Task Force has designed a new protocol for testing Mithramycin against brain tumors. It will consist of a study of 80 to 100 patients whose length of survival will be the only index of drug effectiveness. Results should be available within two years.

Chromomycin A_3, chemically similar to Mithramycin, is also under study.

Wilms' tumor, a cancer of the kidney common in infants and children, was treated solely by surgery and radiotherapy until the last decade. Moreover, the percentage of cures reported by different institutions ranged from 17.6 percent to 40 percent for the years 1936 through 1956.

In the mid-50's Dr. Sidney Farber, Director of Research at the Children's Cancer Research Foundation, Boston, and an invaluable collaborator in National Cancer Institute programs, added the antibiotic Dactinomycin (Actinomycin D) to the surgery-radiotherapy approach. His long-term results, just reported, show that his patients' 2-year survival (in this disease almost always equivalent to cure) has risen from 40 percent to nearly 90 percent. Of 53 previously untreated children without demonstrable metastases, 47 were alive with no evidence of tumor from 2 years to almost 10 years later. An apparent cure was achieved in more than half of 31 children whose disease had already spread to the lungs. Similar findings were recently reported on 34 patients studied by Drs. D. G. Johnson, F. Maceira, and C. E. Koop at the Children's Hospital of Philadelphia. Both groups conclude that Wilms' tumor treated by surgery, radiation, and Dactinomycin should be cured in most instances.

Other solid tumors of childhood.—National Cancer Institute grantees at the M. D. Anderson Hospital and Tumor Institute reported that 5 of 16 children with cancers of the soft tissues, mostly cancer of the muscle fibers, responded temporarily to therapy with vincristine sulfate. The report was recently published by Dr. W. W. Sutow and associates.

In another NCI-supported study, Dr. David H. James and his associates at the St. Jude Children's Research Hospital recently reported that 6 of 6 children with cancer of the muscle fibers responded to concurrent treatment with vincristine sulfate and the antibiotic Dactinomycin. Although one of these responses last only a month, the others were maintained 4 to 12 months.

Neuroblastoma, a malignant tumor of the nervous system, has responded with varying degrees to different forms of chemotherapy. Among the most promising results to date are those achieved by the Southwest Cancer Chemotherapy Study Group sponsored by the NCI. Dr. W. G. Thurman, Chairman of the Writing Committee of the Southwest Group, reported that 24 children with progressive neuroblastoma, no longer responding to surgery or X-ray, were given intravenous doses of the drug cyclophosphamide daily for 8 weeks. Nineteen of the children responded for periods of 1 month to more than 20 months. Ten children had good objective and subjective responses; a few had fair responses.

At the St. Jude Children's Research Hospital, chemotherapy and radiotherapy were successful in reducing the cancer sufficiently to permit its surgical removal. NCI grantee Dr. David H. James and his associates report that one patient treated with vincristine prior to radiation and surgery showed no evidence of neuroblastoma more than 19 months following the treatment. The other patient, treated with vincristine and cyclophosphamide prior to radiation and surgery, was continuing in complete remission 2 months after completion of the treatment.

Retinoblastoma, a malignant-tumor of the eye, usually is found in children under the age of 4; one-third of the cases involve both eyes. It occurs once in approximately 23,000 births and is considered to be a congenital tumor. The aim of treatment is not only to save the life of the child, but to save the vision of at least one eye.

NCI grantee Dr. George A. Hyman and his associates at the Columbia University College of Physicians and Surgeons have reported on 250 children with retinoblastoma affecting both eyes and with an outlook ranging from very favorable to very unfavorable. After treatment with the drug triethylene melamine (TEM) prior to and following radiotherapy, the patients achieved a "useful vision and cure rate" ranging from 85 percent in very favorable cases to 22 percent in very unfavorable cases.

In another published report of NCI-supported work, Drs. Algernon B. Reese and Robert M. Ellsworth of the above institution confirmed the dramatic effect of TEM on retinoblastoma and noted a suggestion of synergism, or additive effect, in the action of combined radiation and chemotherapy. Patients unresponsive to the combination, however, are treated by light coagulation, the light source being a xenon tube.

NCI research career awardee Dr. Edward T. Krementz at the Tulane University School of Medicine and his associates reported on 15 children with retinoblastoma treated surgically and with intra-arterial TEM and radiation. Ten remained alive with no evidence of disease, and with useful vision in the remaining eye. Three patients are living without vision; two have died with widespread retinoblastoma.

Cancer of the adrenal gland.—Several years ago, a drug related to the insecticide DDT, ortho, para' DDD (o,p' DDD), was first reported effective for treating cancer of the adrenal gland by the late Dr. Delbert M. Bergenstal and his associates at the National Cancer Institute, and production of o,p' DDD was sponsored by the Institute. Recent evaluation of a large number of patients by Institute investigators Drs. Adolph M. Hutter[1] and Donald E. Kayhoe[2] indicates that of 59 patients with evaluable, measureable disease, about one-third had objective remission of their cancer lasting a median duration of about 7 months following o,p' DDD therapy.

Cancer of the pancreas.—Preliminary findings by investigators of the Central-Western Drug Evaluation Program have suggested that the candidate drug Tubercidin may be specifically useful in pancreatic cancer. Mixing whole blood with Tubercidin prior to its administration seems to eliminate the problem of toxicity at the site of injection.

Breast cancer.—Ths is the leading cause of cancer deaths among United States women. It will strike 64,000 during 1967 and cause 27,000 deaths. Surgery and radiotherapy are used to treat early forms of the disease. Hormones (androgens and estrogens) and about a half-dozen nonhormonal agents including 5-fluorouracil offer temporary relief to patients with widespread disease.

In an attempt to find more effective agents, the Breast Cancer Cooperative Group is now studying more than 40 new hormonal compounds. In addition, the National Cancer Institute has established a Breast Cancer Task Force, whose activities are described in a separate report.

THREE NEW INTENSIVE STUDY GROUPS FORMED

Upon the recommendation of the National Advisory Cancer Council in November 1966 and with guidance from the Scientific Director for Chemotherapy of the National Cancer Institute, three new intensive study groups are being formed to search out and evaluate all known data on the following types of cancer: 1) lung, 2) colon-rectum, and 3) prostate and bladder.

An indication of the present status of chemotherapy in these three disease areas is reflected in the following brief résumés:

Lung cancer.—This cancer now claims 50,000 lives each year in the United States. A review of data published during the past six years on advanced, inoperable lung cancer indicates that a combination of the drug 5-fluorouracil and radiotherapy produces temporary remissions in some patients with this usually rapidly fatal cancer. At the May 1966 meeting of the American Association for Cancer Research, National Cancer Institute cooperative group member and grantee Dr. F. J. Ansfield and his colleagues at the University of Wisconsin reported that 13 patients who had received this combination had at that time an average survival of 22 months, with three patients living more than five years.

Cancer of the colon and rectum.—There will be 73,000 new cases of this type of cancer in the United States during 1967, more than any other form of cancer except skin cancer. It strikes men and women equally. Although about 44,000 Americans die of colon-rectal cancer annually, most might be saved by early diagnosis and adequate treatment.

In a recent survey of published results in chemotherapy of advanced cancer of the colon, the drugs 5-fluorouracil and 5-fluorodeoxyuridine appear to be the most useful. In a National Cancer Institute grant-supported study, Dr. Donald B. Rochlin of the University of California School of Medicine reported that of 130 patients treated with 5-fluorouracil, nearly half showed an objective response to therapy lasting 2 to 32 months. National Cancer Institute grantee Dr. Fred Ansfield studied 5-fluorodeoxyuridine in 57 patients with colon cancer, almost half of whom experienced remissions lasting an average of a year.

Prostate and bladder cancers.—Apart from reports on the use of female hormones as first suggested in 1941 by Nobelist Dr. Charles B. Huggins and his colleague Dr. Clarence V. Hodges, data on the chemotherapy of prostatic cancer are scant. In a survey of results of treatment with other agents, only one complete remission was noted in a search of six years of medical literature. This was reported by Dr. H. M. Weyrauch and his associates following administration of ThioTEPA; the remission lasted longer than 12 months.

Invasive and disseminated bladder cancers have been notably unresponsive to drug treatment. Some encouraging results, however, have been obtained with

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[1] Now at the University of Rochester School of Medicine, Rochester, N.Y.
[2] Now at the National Institute of Allergy and Infectious Diseases.

multiple, superficial cancers of the bladder. At the Fifth National Cancer Conference co-sponsored by the National Cancer Institute and American Cancer Society, Dr. Ralph J. Veenema of Columbia University College of Physicians and Surgeons reported the usefulness of the local administration of ThioTEPA into the cancerous bladder. He reported that of 38 patients so treated, there was complete destruction of the tumors in 13 patients and partial destruction in 14 others.

Each of the new intensive study groups will be chaired by a non-government cancer scientist prominent in the given biomedical field. National Cancer Institute funds will be made available to allow him and his committee to meet as frequently as needed, and to cover secretarial expenses. The Chairman of each Intensive Study Group will be named to membership on the Solid Tumor Task Force, and executive secretaries of the Intensive Study Groups will collaborate directly with the Institute's Scientific Director for Chemotherapy.

Chairmen of the Study Groups will be encouraged to pursue avenues of their own choosing to develop the information needed for an integrated, multidiscipline, problem-solving attack on the individual cancer types. Cause, prevention, and early detection may be studied as well as treatment. It is anticipated that the special physiologic and biochemical characteristics of the organ or body area involved will be thoroughly investigated in the search for therapeutic methods. The natural history of the disease will be thoroughly explored. The role of surgery and radiotherapy in treating these cancers will be defined. The additive effects achieved by combining surgery, radiotherapy and chemotherapy will be investigated.

Information developed on the growth cycle of each individual cell type and therefore its period of special vulnerability to chemotherapy and radiotherapy will be evaluated. Pharmacologic studies on the best route of drug administration, and the most effective drug dose levels, schedules, and combinations will be conducted for each disease.

CONCLUSION

More than 300,000 Americans will die of cancer during 1967. The National Cancer Institute, responsive to the needs of the American people and to the suggestions of the Congress, has launched an effensive against the major killers. Lung cancer, colon-rectal cancer, and cancers of the prostate and bladder are the newest targets of National Cancer Institute scientists and their collaborators in the biomedical community, in addition to the continuing attack on the leukemias, lymphomas, breast cancer, brain tumors, choriocarcinoma, and other cancers. Using information gained in almost 30 years of research and vigorously pursuing the leads of the past year or so, the National Cancer Institute is pressing forward in this task as intensively as the nation's scientific and financial resources permit.

FELLOWSHIPS

Mr. NATCHER. For research grants you have a token increase, but for fellowships it looks like you are straining considerably, Doctor, to show any increase at all.

On new awards you show an increase of one, going from 146 to 147, and a reduction of $192,000. How do you explain this, Doctor?

Dr. ENDICOTT. As Dr. Shannon indicated yesterday, the necessity for living within a budget leaves one with some difficult choices. This, as you say, is not much of an increase but it is about the best that could be done under the circumstances.

TRAINING GRANTS

Mr. NATCHER. In training you have a very small increase in the number of programs from 157 to 165, but a decrease of nine in the number of new programs.

From what we have been hearing and reading, Doctor, it should be going the other way; should it not?

Dr. ENDICOTT. Yes, sir; it definitely should. Probably the most urgent need now, if there is to be real meaning to the regional medical

program for heart cancer and stroke, probably the most urgent need of all is the training of physicians for positions in the medical centers. It is very difficult for a medical center to share its knowledge with the outlying parts of the regions if the knowledge is not in the center.

DISTRIBUTION OF CANCER CENTERS

This has been a matter of great concern to us, growing concern. The distribution of expert clinical research manpower in the cancer field is very badly skewed in this country. The major cancer centers for the most part are on the east coast from Washington, D.C., north. In the entire Mississippi Basin there are only two really major cancer centers. One is in Houston and the other one is in Madison, Wis.

When you have said that, you have just about said it. There are no real cancer centers on the entire west coast and the whole Rocky Mountain-intermountain area.

Mr. SMITH. What causes that kind of distribution?

Dr. ENDICOTT. This puzzles me. Of course they are where they are because someone has taken initiative, and usually this has taken the form of creating a cancer institute. I could mention some of them, one at Buffalo, Roswell Park Memorial Institute, is supported heavily by the State of New York.

The Sloan-Kettering Institute in New York City was created by the efforts of Mr. Sloan and Mr. Kettering under the goading of a very vigorous man by the name of Cornelius Rhoads. Dr. Farber himself almost singlehandedly created the Children's Cancer Research Foundation in Boston; the State of Texas took the initiative in creating the splendid center in Houston as a part of the University of Texas, the M. D. Anderson Hospital.

And the University of Wisconsin, a very farsighted president of the university, I think, took the initiative in developing a basic research institute called the McArdle Laboratory and developing a cancer research hospital some 15 years ago.

Once these are started they serve as a nucleus and people interested in the disease find others interested in it and you get a collection until you finally have what you might call a critical mass and you have an organization that is big enough to really tackle this kind of a problem.

Most medical schools have very, very small cancer programs. It is quite disturbing to me that many of them do not have a trained radiation therapist in the whole medical school.

There are a number of medical schools in which there is not a man on the faculty I would regard as an expert in drug treatment of cancer.

CLINICAL TRAINING PROGRAM

Now we have set about trying to do something about this in a very positive way, using a variety of techniques. And I feel that we can create the institutional situation which will make a place for these people, but the other part of the job is to train them, and to this end a year ago we launched a new program in clinical training. This program is aimed at the institution itself, it is not intended to provide stipends for students. We are attempting to improve the capability of the entire institution to provide better cancer training for everyone who is going through it—doctors, nurses, technicians, scientists, and so forth. The program is just getting underway.

I think, given time, we can do what must be done. Any delays now will inevitably be reflected in delays in the time when we will really be in a position in the cancer area to implement the spirit of the regional medical program.

GEOGRAPHICAL DISTRIBUTION OF CANCER

Mr. HULL. Dr. Endicott, is cancer more prevalent in one section of the country than in others?

Dr. ENDICOTT. It is slightly more prevalent in cities, it is slightly more prevalent in the Northeast, slightly less prevalent generally in the South, although there are some localized exceptions to this.

New Orleans, for example, has a rather high cancer incidence. There is some difference in this country but the big differences are between this country and other countries. There you see very spectacular differences.

DIRECT OPERATIONS

Mr. NATCHER. You have an increase of about $4.7 million and 40 positions for your direct operations. Tell us why you need this increase, Dr. Endicott.

Dr. ENDICOTT. The positions are as follows: We need an additional surgeon, we need a radiologist, we need an immunologist, we need a senior biologist, and some technicians to support them.

In the collaborative research area we are opening this year a new—it is already opened but we are expanding—a program at the Public Health Service Hospital in Baltimore where we now have about 100 beds for the study of cancer patients. We have renovated a nurses home to use as a pharmacology laboratory, and this will become an important new drug evaluation center. We also need quite a number of people and equipment to get that show properly operating, including pharmacologists, radiologists, a deputy chief, toxicologist, immunologist, virologist, and some supporting personnel.

Mr. NATCHER. You feel this increase is necessary, Doctor?

Dr. ENDICOTT. Yes, sir; I certainly do.

Mr. NATCHER. Mr. Laird?

Mr. LAIRD. Mr. Chairman, you covered this very well.

INSTITUTIONAL SETTING FOR CANCER RESEARCH

Dr. SHANNON. There is one comment I would like to make on the doctor's testimony that I think is very important for the committee to appreciate.

Cancer research, as a combination of studies, is hampered by the fact that it does not fit conveniently into the academic structure of any universities or medical schools.

Consequently, as Dr. Endicott pointed out, if one is to have a vigorous program in cancer research in our medical institutions, one has to make other institutional arrangements to provide for permanent, high level, competent scientists of a wide variety who can bring together varying discipline structures in the schools.

The concentration of arrangements of this sort in the Northeast is probably reflective of the early start that the Northeast had in the biomedical sciences beginning in the late 1920's and 1930's. The total

west coast science plants developed subsequent to the beginning of World War II. For instance, the medical school in Seattle was established in 1945.

The normal development of these medical institutions involves, first, a development of the essential areas for conventional teaching in all diseases, but they are now developing to the point where special studies can be made for special programs.

Dr. Endicott spent the better part of November and December of last year going from institution to institution in order to determine what the capability of each institution was for growth at this particular time. Some of the recommendations he made to us relative to last year's budget and this year's budget were the result of personal assessments of the institutional capabilities across the Nation.

Dr. Endicott's projections, therefore, are based on real need, on the one hand, and personal knowledge, on the other hand, of specific capabilities of many institutions.

CAUSES OF LUNG CANCER

Mr. NATCHER. Thank you, Dr. Shannon.

Dr. Endicott, I was very much interested in that portion of your statement which appears on page 2 wherein you state, in part, that lung cancer is still the leading cause of cancer deaths in this country, particularly among men.

Further over in your statement you discuss the question of cancer of the cells. You make a statement to the effect, Doctor, that although research has since ranged over much wider fields, the ultimate solution to the cancer problem is probably still locked in the cell. I believe that appears on page 7.

Dr. ENDICOTT. That is right.

Mr. NATCHER. Do you know what causes lung cancer?

Dr. ENDICOTT. There are a number of things which cause lung cancer. In some the proof is better than in others.

The first evidence related to radioactive ores which were inhaled by the miners in Europe.

Subsequently it was clearly established that the inhalation of certain chromate dusts produces lung cancer.

It is now quite clear that the gases given off in the coking process produce lung cancer. Workers in the coking operation who work topside have a spectacularly higher incidence of lung cancer. There is really no room to doubt that smoking cigarettes increases lung cancer, but there are a number of factors involved.

Mr. NATCHER. You say there is no doubt that smoking of cigarettes causes lung cancer. Can you provide for the committee at this time the research that proves this?

Dr. ENDICOTT. I could supply an enormous amount of evidence for the committe if you wish it.

Mr. NATCHER. Briefly just give us some of this, Doctor.

You recall back during the days of the report on smoking—was there not a statement in that report to the effect that the burning process of a cigarette showed the same thing as the burning process of spinach? Don't we have something in there to that effect?

Dr. ENDICOTT. I don't recall that specific statement.

Mr. NATCHER. The same thing takes place in the burning of spinach that takes place in the burning of tobacco, and that the effects might be the same. Do you recall any of that, Dr. Endicott?

Dr. ENDICOTT. There is extensive evidence that burning of organic materials of a great variety produce in the process of incomplete combustion certain compounds which are powerful chemical causes of cancer. This occurs in the burning of fossil fuels, such as petroleum. It occurs in the burning of coal. I don't know about spinach, but I am willing to predict flatly that you can produce this by burning spinach or lettuce or hickory or almost any plant product.

Mr. NATCHER. Is that what causes lung cancer, the burning process and the results from the burning?

Dr. ENDICOTT. There are a number of agents which can be recovered from the tar of cigarette smoke which are capable of producing cancer. Part of them are created in the burning process. Part of them are already present in the tobacco and are simply carried over as particulate matter in the smoke.

As an example of this, there has been enough fallout of certain radioactive materials which are concentrated in the tobacco leaf—polonium is such a material—that is carried over in the smoke. It is not created by the burning.

Some of the organic compounds are created by combustion.

Mr. NATCHER. You mentioned tar and one or two others. What other constituents of smoking might be responsible for lung cancer other than those you have mentioned?

Dr. ENDICOTT. If you will permit me to pass this question on to one of the world experts——

Mr. NATCHER. I would like you to handle it for a while. Let us discuss it a little and then we will let you pass it to Dr. Kotin.

You don't want the Surgeon General to handle this any more. We had him the other day.

Dr. ENDICOTT. All right.

Mr. NATCHER. Are there any other constituents involved?

Dr. ENDICOTT. There is a series of constituents of tar from cigarettes that are carcinogenic. They are carcinogenic in a variety of situations.

I can give you the chemical groups. I would have to supply the detailed chemical names for the record.

Mr. NATCHER. Suppose you do that at this point.

Dr. ENDICOTT. There is one class called polycyclic hydrocarbons.

Then there are heterocyclic hydrocarbons.

Then there is a series lumped together as the alkylating agents, nitrosamines, lactones.

There are some highly unstable materials called free radicals which exist in time only, short periods, combining with something.

We have polonium 210, various trace metals, nickel in particular; some alkaloid oxidation products, cotinene, various peroxides, phenols, and polyphenols, and then there is another group that are not carcinogens in themselves but in the presence of other carcinogens increase the effect.

The three categories are phenols, polyphenols, and aliphatic hydrocarbons.

Then there is a series of chemicals which are neither cocarcinogens or carcinogens but are irritants which may have an effect by weaken-

ing the resistance of the lining epithelium of the respiratory tract. These include aldehydes, various acids, and various of the oxides of nitrogen.

There are some aromatic amines found in the tar which are carcinogenic and have their action in the bladder.

There is a very toxic agent which has a direct toxic effect on living cells, acetonitrile.

RESEARCH ON SMOKING AS A POSSIBLE CAUSE OF CANCER

Mr. NATCHER. Dr. Endicott, can you tell me the research specifically that proves this?

Dr. ENDICOTT. That proves these are carcinogenic?

Mr. NATCHER. Yes.

Dr. ENDICOTT. Yes, sir; I can supply that for the record.

(The information follows:)

The section on smoking and health is submitted for inclusion in the record as a joint report from the National Cancer Institute and the Division of Environmental Health Sciences.

TOBACCO AND HEALTH (LUNG CANCER)

The evidence suggesting a role for cigarette smoking in the causation of pulmonary disease derives from three main areas of study.

1. Epidemiological data indicate that cigarette smokers are at increased risk to the development of lung cancer, bronchitis, and emphysema. A similar epidemiological association is seen in urban residents exposed to polluted city air.

2. Chemical analytical studies have established the presence of compounds in cigarette smoke which are (a) experimental laboratory carcinogens, (b) co-carcinogenic agents, and (c) chemical and physical irritants which can modify normal ciliary function and qualitatively and quantitatively alter the mucus secreted by the cells lining the respiratory tract.

3. Biological studies have shown that cigarette smoke condensate and certain of its fractions are capable of producing cancer in experimental animals when applied by skin painting techniques, injection techniques and direct installation in the respiratory tract.

Over twenty independent retrospective epidemiologic surveys have demonstrated an association between cigarette smoking and lung cancer in men. Two major prospective epidemiologic surveys have been undertaken, one in the United States and one in the United Kingdom and these latter two surveys have corroborated the findings of the retrospective studies in demonstrating this association. In assessing the increment of contribution of cigarette smoking to the total incidence of lung cancer as currently observed, it is necessary to recognize and evaluate other associations which fulfill the criteria for suspicion in lung cancer causation. The epidemiologic evidence describing an association between the exposure to general air pollution and lung cancer leaves little doubt that those who live in big cities, conurbations and industrial areas have a higher risk for lung cancer than those living in rural areas.

Further there have been identified a series of industrial and occupational factors which appear to have a causal role in the development of lung cancer. These include:

1. Arsenic
2. Asbestos
3. Beryllium
4. Chromium
5. Coal and gas
5. Nickel
7. Radioactive ores

On the basis of epidemiological association alone, cigarette smoking would appear to be the most potent of the environmental influences yet studied, although the multiplicity of factors associated with increased risk is at present a confounding factor in any attempt to arrive at a finite percentage contribution. The asso-

ciation appears unequivocal and its causal implications are supportable; the latter particularly, in light of the most recent epidemiological findings indicating that cessation of smoking is associated with a reduction in the risk to lung cancer.

From an analytical viewpoint, compounds belonging to chemical groups containing carcinogenic members have been identified. These include:

1. Carcinogenic polycyclic aromatic hydrocarbons
2. Carcinogenic heterocyclic compounds
3. Alkylating agents of both the nitrosamine and the lactone type
4. Radioactive elements
5. Trace metals
6. Free radicals

While not all of the individual members of each group listed above are carcinogenic, carcinogenic members have been identified in each.

Compounds belonging to the general group of carcinogens include:

1. Phenols and polyphenols
2. Aliphatic hydrocarbons

Compounds belonging to the group of irritants include:

1. Aldehydes
2. Acids
3. Oxides of nitrogen

Bioassay studies have been performed on total smoke condensate, as well as individual fractions of condensates with the production of skin cancer following painting, connective tissue tumors on injection and lung tumors following direct installation into the lung. It is to be recognized that these agents have been applied in concentrations significantly greater than those occurring under natural use of tobacco and by means of application other than smoking and inhalation. However, these agents have been applied under strict laboratory conditions, usually as a single agent exposure in contrast to the human situation where daily living results in exposure to a highly complex environment with multiple sources of carcinogens, cocarcinogens, and irritants.

The cocarcinogens in tobacco belonging to the group of phenols and polyphenols have been under laboratory conditions shown to be cocarcinogenic; i.e. they are capable of enhancing the action of a carcinogen so that concentrations of the latter which are incapable of producing cancers alone, are transformed or potentiated so that they achieve cancer producing levels. The cocarcinogenic compounds alone are incapable of inducing cancer.

Irritants though incapable of initiating cancer, facilitate the sequence of events which result in cancer induction by interfering with the normal flow of mucus covering the lining cells of the lung. Mucus flow is accomplished by the propulsive beat of whip-like processes on the cells lining the lung, called cilia. Ciliary action is significantly interfered with often to the point of total paralysis by cigarette smoke as well as certain of is constituents.

The following represents in summary form the components of the body of data suggesting a causal relationship between cigarette smoking and lung cancer.

1. An increased risk to lung cancer associated with cigarette smoking with the risk relatively proportional to the amount and duration of smoking.

2. The identification of compounds of cigarette smoke which are capable of a) producing cancer in experimental animals, b) acting as cocarcinogens, and c) interfering with ciliary action and mucus flow, as well as qualitatively and quantitatively altering the mucus secretion of the lining of the lung. This effect on cilia and mucus deprives the lung of its normal defense mechanism whereby the continuous flow of mucus from the outer portions of the lung to the throat prevents the local accumulation of inhaled materials. This dynamic condition deprives these agents of an opportunity to enter the cell and produce adverse effects. As noted above, there are other environmental experiences possessing similar associations, similar chemical, physical and physiological properties and similar tumor inducing properties.

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Mr. NATCHER. Why does not everyone who smokes get lung cancer?

Dr. ENDICOTT. Of course, I don't know. This is a general observation with almost any form of cancer-causing agent—if you expose the population, the entire population, to a given cancer-causing agent only some of those exposed develop cancer.

If we understood this I think that this in itself might be one of the most important breakthroughs that could be made, but I don't know why.

Mr. NATCHER. Is it not likely that there are other factors which play a role in the disease?

Dr. ENDICOTT. In lung cancer?

Mr. NATCHER. Yes.

Dr. ENDICOTT. Oh, yes, sir. I have mentioned several of them. For

example, we have a study in progress in the Colorado Plateau amongst uranium miners. There is a substantial increase in risk of lung cancer if you mine radioactive ores.

In improperly controlled chromate industries where chromate dust is around it is increased.

I mentioned the coking process.

In the process of cracking petroleum for the preparation of gasoline or refining petroleum for various purposes, unless this process is very carefully contained there is a major risk.

There was a group of Japanese who worked on the manufacture of mustard gas before and during World War II, and there is a very high incidence of lung cancer among workers in that factory. Therefore the answer is yes, sir, there are many causes.

VIRUSES AND LUNG CANCER

Mr. NATCHER. Is it possible that viruses play a very important role, too?

Dr. ENDICOTT. It is possible, and there are those who have speculated that part of the increase in lung cancer might be attributed to epidemics of influenza which occurred around the time of World War I. However, this does not fit the pattern of distribution of the disease as we see it today.

Mr. NATCHER. In addition to the influenza we had back during World War I, do we have other lung infections which might play a major role, too?

Dr. ENDICOTT. This is entirely possible.

I was going to turn to Dr. Kotin, who is on my staff and moving to Carolina to head up the environmental health center, because he has had so much experience and done so much research in the field.

He did an interesting piece of research a few years ago in which he succeeded in producing cancer by adding or superimposing an influenza infection on exposure to chemical carcinogens which, without the influenza, did not produce the cancer in animals. That was probably the first work of that sort.

Mr. NATCHER. You might want to turn to Dr. Kotin.

Do you want to add anything further?

Dr. KOTIN. The role of viruses?

Mr. NATCHER. Any previous lung infections as far as playing a major part.

Dr. KOTIN. I don't know that we can say a major part but certainly we do know lungs that have some prior abnormalities as a result of the disease are more prone to localized chemical carcinogens to react with them and therefore are more likely to have a cancer develop than a lung similar in every other way except for the fact he doesn't have this lung infection.

Mr. NATCHER. Let me ask you the same question I asked Dr. Endicott.

Do you know what causes lung cancer?

Dr. KOTIN. I know agents that are associated with increased risk in lung cancer. There is a series of environmental experiences which when participated in by the population, or segments of the population, results in their having a greater likelihood of developing lung cancer.

At the cellular level, the actual mechanics involved in alteration of the cells, as Dr. Endicott points out, we don't know this.

However, we do know that the environmental agents which are associated in the increased risk for lung cancer are substantively important.

Development of a cancer is the development of a series of sequential events. We know in those instances where we have been successful in modifying the environment or removing the environment, or moving people from the environment, that a reduction of the risk has been brought about. The cause-effect relationship is one of the links in the chain.

RELATIVE EMPHASIS GIVEN TO TOBACCO AS CAUSE OF LUNG CANCER

Mr. NATCHER. Dr. Kotin, are you and Dr. Endicott and others pointing your finger at these other elements which might enter into it as well as tobacco or are you just confining your attention to tobacco and saying that tobacco causes lung cancer?

Dr. KOTIN. I assure you that tobacco represents only one segment of a very broad approach.

As you pointed out so very importantly, the attack rate, even in the class of smokers who presumably have smoked long enough to enter this category, is a very low one relatively speaking. One has to assume that other factors are operating in sequence which ultimately develops in a cancer.

To approach any one agent, Dr. Endicott mentioned the high risk asociated with chromate exposure, coking operations, radioactivity, these other experiences themselves all are factors which we know can cause an increased risk in lung cancer and we are trying to see where they fit into the overall national pattern of the disease.

Certainly we are concerning ourselves with virtually all areas that have some degree of suspicion in terms of contributing to the problem.

NUMBER OF DEATHS FROM LUNG CANCER

Mr. NATCHER. I believe you and Dr. Kotin, Dr. Endicott, would agree with me that it is true that only a relatively small number of smokers actually get lung cancer. Is that true?

Dr. KOTIN. If I may say, by far the greater number of smokers do not get lung cancer.

Dr. ENDICOTT. 50,000 is a pretty large number of deaths. This year I anticipate there will be 53,000 deaths deaths from lung cancer, not all attributable to cigarettes but certainly a substantial part of it; 50,000 is a small number compared to the number of people who smoke, but 50,000 deaths is not a small number.

Mr. NATCHER. You say that 50,000 who died, those you have just mentioned, died as a result of lung cancer which was brought about as a result of smoking. Is that right, Doctor?

Dr. ENDICOTT. No, sir, that is not what I said. I said there will be 53,000 deaths of lung cancer this year as far as we can best estimate.

Out of that group a percentage will never have smoked. Perhaps on the order of 10 percent of the patients who die of lung cancer this year will never have smoked in their lives.

The others will have smoked, and most of them heavily and for a long period of time, at least if the pattern stays as it has been in the past few years.

The risk relatively is, I suppose—well, you might liken it to the risk of driving an automobile. The number of deaths from motor vehicle accidents will be almost precisely the same this year as the number of deaths from lung cancer.

Mr. NATCHER. Dr. Endicott, I believe the figures show there are some 70 million people who smoke. Is that about right?

Dr. ENDICOTT. Yes.

Mr. NATCHER. Do you agree with that, too, Dr. Kotin?

Dr. KOTIN. Yes, sir.

Mr. NATCHER. Assuming that the number of people who die from lung cancer is relatively small as far as pointing your finger directly at tobacco. Susceptibility of the individual might be a highly important factor.

Would you agree with that, Dr. Endicott?

Dr. ENDICOTT. I certainly would.

Mr. NATCHER. Do you agree with that, too, Dr. Kotin?

Dr. KOTIN. Yes, sir.

SMOKING AND EMPHYSEMA

Mr. NATCHER. Dr. Endicott, has it been scientifically established that smoking actually causes emphysema in your opinion?

Dr. ENDICOTT. I think myself that the evidence for this disease is not as well developed as in the case of cancer. We know very little at this point in time about the disease emphysema, whereas cancer has been extensively studied, so I can give you a long list of specific chemicals that cause cancer.

There has been so much less work done on the whole disease of emphysema that it is pretty much of an unknown.

The evidence is statistical and it relates to the increased incidence of this disease in heavy smokers as compared to nonsmokers, but this evidence is not supported by anything like the amount of contributory laboratory evidence that implicates the cigarette in lung cancer.

SMOKING AND HEART DISEASE

Mr. NATCHER. Has it been scientifically established in your opinion that smoking actually causes heart disease?

Dr. ENDICOTT. The evidence varies with the type of heart disease. There are some relatively uncommon vascular diseases that have been known to be associated with the use of tobacco for a good many years. One of these is the vascular disease especially common in the Jewish race and results in gangrene of the extremities.

The association here is very strong, indeed.

In some of the other cardiovascular diseases the relationship is much the same as I mentioned in emphysema where the background knowledge of the disease itself is not so fully developed as in the case of cancer when one establishes the risk by an observation of the population.

Mr. NATCHER. If there is some question about tobacco causing emphysema and heart trouble, do you believe it is justifiable for the Public Health Service to imply in its literature, or for any of the officials of the Public Health Service to state or to imply that smoking causes these diseases when it is uncertain?

Dr. ENDICOTT. I am perfectly prepared to state with conviction and no apologies that excessive smoking is causing excessive death from lung cancer in the United States today.

Mr. NATCHER. What about emphysema? I am directing this question to you mainly from the standpoint of emphysema and heart disease. In these two instances is it justifiable in your literature—and you will agree with me that your literature points the finger at a great many things other than lung cancer from the standpoint of smoking—is it justifiable for the Public Health Service to take this action?

Dr. ENDICOTT. Yes, sir; I think it is justifiable to indicate the excess risk of these diseases associated with excessive smoking.

Mr. NATCHER. When you don't have much to base it on, Doctor?

Dr. ENDICOTT. The evidence obtained by studying populations in my opinion is as valid as any one of a number of types of research. It is reproducible, it happens again and again, if the chemical is present, the incidence is high. If the chemical is absent, the incidence is low. To me this is as convincing a type of scientific evidence as the more direct observation of taking a specific chemical, injecting it into a mammal, and getting a tumor where you inject the chemical. It is a different kind of scientific study but it certainly is scientific.

ROLE OF GOVERNMENT IN SMOKING EDUCATION

Mr. NATCHER. Dr. Endicott, in regard to periodicals, literature, and other publications what is the proper role for the Government to take in regard to smoking education?

Dr. ENDICOTT. My feeling about this is that a health agency, recognizing a serious health hazard, has an obligation to the public, a duty to the public, to warn the public, and if in my opinion it is a really effective health agency it must go beyond that and try to eliminate the hazard.

I would feel very remiss in my duties, having established that chromate dust increases the risk to lung cancer, if I didn't put as much pressure as necessary on the chromate industry to contain the process and reduce the exposure.

Therefore I would say yes, sir, the Public Health Service has a duty to warn the public and to go beyond that and try to solve this problem. I think that is why we are in business, sir.

PROGRAM TO DEVELOP SAFER CIGARETTE

Mr. NATCHER. Are you familiar with the article that recently appeared in the National Observer that reported, I believe, that the Public Health Service was urging a 10-year, $50 million program to develop a safer cigarette?

Dr. ENDICOTT. No, sir; I have not seen that article.

Mr. NATCHER. Do you know anything about any program that is underway along this line at this time?

Dr. ENDICOTT. Yes, sir; I do.

Mr. NATCHER. I wonder if you would provide the committee with details as far as the program is concerned?

Insert that at this point in the record.

(The information follows:)

There is reason to believe that the development of a less hazardous cigarette is potentially within reach. While it may be argued that at present we are not necessarily aware of all toxic components or irritants in cigarette smoke, sufficient data and technological information are available to permit delineation of a research program at this time. Present knowledge of constituents of cigarette smoke has permitted an identification of several classes of compounds that may be related to the toxicologic effect of cigarette smoke. Moreover, it is now technically possible to remove or reduce certain constituents that are thought to be responsible in part for the hazardous properties of cigarette smoke. For certain other constituents, techniques can be developed.

In the view of the Division of Environmental Health Sciences of NIH, research aimed at developing a less hazardous cigarette can appropriately be pursued in the following directions:

(A) Further elaboration of principles on which to base processes for reducing the load of carcinogenic and co-carcinogenic materials;

(B) Studies aimed at minimizing possibility that treatments of tobacco may introduce new and unexpected hazards such as formation of carcinogenic nitrosamines;

(C) Improvement of cigarette filters and other means for reducing exposure to hazardous components of cigarette smoke;

(D) Continued exploration of techniques for protecting the tracheobronchial tree from irritants in smoke by filtration and other means;

(E) Identification of conditions that may aggravate the hazards associated with cigarette smoking, such as upper respiratory infection, smoking in air contaminated with specific types of dusts, etc.;

(F) Increased efforts to learn about pyrolysis and oxidation products of pesticides used on tobacco that have high persistence and to search for low-residue replacements;

(G) Determination of potential toxicity produced by fungi found frequently in association with tobacco;

(H) Identification of metabolic characteristics of hosts with apparently higher threshold of resistance to hazardous components of cigarette smoke.

STATEMENT OF DR. CHARLES LEMAISTRE ON THE CAUSE OF LUNG CANCER

Mr. NATCHER. Several months ago I read a statement to the effect that a Doctor Charles LeMaistre, a member of the Surgeon General's Advisory Committee on Smoking said that some researcher in Texas had discovered what it was in cigarettes that was responsible for lung cancer.

Can you tell us about this?

Dr. ENDICOTT. I am sorry, sir. That doesn't ring a bell with me at all.

Mr. NATCHER. Dr. Kotin?

Dr. KOTIN. Denials don't get the front page coverage that a statement does. Dr. LeMaistre called a press conference the next day to essentially deny that this is what he had said, that he had been overquoted, as it were.

The research work he was referring to was work that was going on concerned with selectively removing some of the constituents of cigarette smoke which at least chemically are suspected in induction of cancer. This is where the situation is right now.

I have talked to Dr. LeMaistre since then and he verified the fact that the reporter did not quote him exactly correctly.

VIEWS OF THE DIRECTOR OF THE CANCER INSTITUTE ON SMOKING

Mr. NATCHER. Dr. Endicott, the smoking question has been with us for some years now. What do you as a distinguished cancer scientist believe should be done about it?

Dr. ENDICOTT. Well, sir, I must confess that I have been disappointed in the effectiveness of educational campaigns not only in this country but in other countries, and I am inclined to think that some other approaches must be tried.

Whether a safe cigarette will ever be possible is a matter only for speculation, but if 70 million people are going to smoke them and if we know that there are materials carried into the individual in the smoke which are potentially dangerous, I have felt for some time that we ought to tackle this problem head on, find out what it is in there that is bad, and insofar as it is humanly possible get it out of there.

It seems to me such a simple and obvious thing that I am suprised anyone would question it. To some extent this is a straightforward technical problem, just like the problem of making stack exhausts safer for the community.

We are already engaged in research of this sort, particularly at this stage, in identifying the suspect chemicals in the cigarette so we will begin to know the magnitude and general nature of the problem.

I for one feel that the human race being what it is that the place to tackle this problem is the technical attack on the cigarette.

Mr. NATCHER. Thank you very much, Doctor Endicott.

Mr. Shriver?

NATIONAL EXPENDITURES ON ELIMINATION OF CANCER

Mr. SHRIVER. You and others have brought to us a very fine presentation here this morning.

The only question I have is this: About how much money is being spent in this country in connection with the elimination of cancer? I am talking about the American Cancer Society, individual hospitals, and so forth. What is the total effort?

Dr. ENDICOTT. If you divide cancer research into major components, I would say there is something on the order of $250 million being spent on cancer research in this country this year from all sources. At least half of this is aimed at the management of the patient who has cancer.

Probably on the order of 30 percent of this is aimed at understanding the basic biology surrounding the cancer process, and perhaps the rest is directed more or less directly toward prevention of cancer.

Mr. SHRIVER. In your Institute what proportion is spent towards elimination research?

Dr. ENDICOTT. In our Institute we probably devote nearly half of our money to prevention. This has been a deliberate decision on my part. I felt there was not enough emphasis on the preventive aspects of the disease and I have been very deliberately, with the help of Dr. Kotin, mounting a very large program in the prevention side.

Mr. SHRIVER. How much does the American Cancer Society receive every year?

Dr. ENDICOTT. The American Cancer Society—their drive is going on this month—last year received about $50 million.

Not all of this goes for research, of course. They spend a great deal of money on public education, professional education, and on services to cancer victims. About 25 percent of their money goes to national headquarters and most of that is spent for research. An additional amount is spent in the local chapters and at the divisional level for research in those divisions.

I would think out of the $50 million probably something on the order of $20 million would be spent for research. This is in all aspects of cancer.

Mr. SHRIVER. I assume there is considerable evidence in other countries of this same work?

Dr. ENDICOTT. In other countries, notably England, the Scandinavian countries, Russia, and Japan. The Russians are deliberately developing cancer research as a national policy and have created a number of cancer institutes within the last few years.

Mr. SHRIVER. That is all, Mr. Chairman. Thank you.

Mr. NATCHER. Mr. Smith?

RELATION OF THE INSTITUTE TO THE NATIONAL CANCER SOCIETY

Mr. SMITH. To what extent is your activity and are your decisions as to the mix influenced by the money spent by private associations?

Dr. ENDICOTT. Very much influenced. Of course, this happens almost automatically because if a major new source of funds for a specific purpose is identified then this eases the demand on our general fund, so to some extent this is self-adjusting.

We keep a very close eye on the overall distribution of cancer effort.

Mr. SMITH. Do you watch it carefully to see how much the American Cancer Association's contributions total?

Dr. ENDICOTT. Yes, sir. I am on the Board of Directors of the American Cancer Society.

Mr. SMITH. Does this influence what you will do with your money?

Dr. ENDICOTT. Yes. There is an extremely close relationship. As I say, I am a member of the Board of Directors of the American Cancer Society. Members of my staff serve on all of their technical advisory committees. They always have two or three representatives at meetings of the National Advisory Cancer Council where grants are reviewed.

We are in constant communication.

FUNDRAISING COST OF AMERICAN CANCER SOCIETY

Mr. SMITH. What percentage of their money is loading charges? In other words, they have costs of collecting, distributing, and so forth.

Dr. ENDICOTT. The American Cancer Society collection program is by volunteers. They do not employ professional fundraising organizations to raise their funds.

Mr. SMITH. There are still costs of collection and distribution.

Dr. ENDICOTT. Costs in terms of staff, literature, and so on.

I would be very happy to get the precise figure on that and supply it for the record. I don't know.

It is amazingly low.

(Information follows:)

FUNDRAISING COST BY AMERICAN CANCER SOCIETY

Fundraising costs were obtained from the Amreican Cancer Society for the year ending August 31, 1966. Their expenditures for fund raising were $5,198,686, or 10.3% of the annual contribution and legacy income of $50,264,475.

Mr. SMITH. Although their total expenditure is small compared to yours, would you be able to say that the money they spend pretty much replaces money that the Government would spend?

Dr. ENDICOTT. Very definitely. In the research area if their concepts to the approach to the problem are similar to ours they will entertain research proposals in any area and we will entertain them. Many of our projects are jointly supported.

If the American Cancer Society went out of business today there would be $20 million worth of cancer research knocking at my door tomorrow for support, and vice versa.

RELATION OF LUNG CANCER TO RESPIRATORY DISEASE

Mr. SMITH. Apparently the incidence of cancer is greater among persons who have suffered from serious respiratory diseases. Is that true?

Dr. ENDICOTT. I do not believe that total incidence of cancer is related in any way clearly to respiratory diseases.

Mr. SMITH. You mean persons who have had pneumonia, for instance, would not have a greater incidence of cancer than those who have not had it?

Dr. ENDICOTT. I am not aware of any figures which would tie this down with any certainty.

One of the problems, of course, in trying to associate respiratory disease with cancer is that it is almost impossible to find any man, woman, or child who hasn't had respiratory disease, so one of the things you lack is a control group.

Everyone sooner or later has respiratory disease, and most people many times.

Mr. SMITH. Don't you determine whether there is a relationship?

Dr. ENDICOTT. It has been done with specific kinds of cancer. Studies have been made to attempt to associate tuberculosis, for example, with lung cancer.

Mr. SMITH. Perhaps Dr. Kotin can respond to that.

Dr. KOTIN. First of all, the question is difficult to answer because so many of the environmental experiences that are associated with an increased risk in lung cancer are associated with an increased risk to noncancerous diseases of the lung.

For instance, living in the city carries with it an increased risk of bronchitis, emphysema, as it indeed carries an increased risk for lung cancer, so a separation of the two in terms of which came first is a little difficult.

I think the question is very proper in the sense that there is in patients with lung cancer evidence, more than in patients without lung cancer, of antecedent lung diseases. This is all we can say now.

Whether this reflects a casual relationship between the preceding lung disease and the eventuating lung cancer we cannot say.

In answer to the last part of the question, yes, there is extensive——

Dr. ENDICOTT. I misunderstood you. I thought you were talking about cancer in general.

COORDINATION OF RESEARCH AMONG NIH INSTITUTES

Mr. SMITH. No. This leads to the question I wanted to ask. To what extent are your activities coordinated with those researchers who are working on respiratory diseases so that you can further identify leads in this area?

Dr. ENDICOTT. In general the same men study both conditions so that they do a lot of the coordinating themselves. The man who is the respiratory physiologist studies a number of different types of diseases of the lungs.

Mr. SMITH. Is this a separate Institute, or does that have significance?

Dr. ENDICOTT. Dr. Shannon may want to answer this. There are reasons for a number of Institutes to study the respiratory system—the Infectious Disease and Allergy Institute, the Heart Institute, the Cancer Institute, and Dr. Kotin's new Division.

Mr. SMITH. I will ask Dr. Shannon. Before you reply perhaps I should indicate another thing I am leading up to, and that is whether having separate Institutes tends to cause inefficiency.

Dr. SHANNON. I don't believe so. The lack of such an obstacle is shown if you receive a copy of a recent report on chronic respiratory diseases developed by the staffs of several Institutes that have broad commitments to these problems, and also by other bureaus of the Public Health Service that have control activities which make use of such knowledge in operational situations.

This report represents the attitude of the Public Health Service toward respiratory illnesses.

There are many areas which may be given prominence in one Institute but which are also reflected in others.

Mr. SMITH. Would the same researchers be working in both Institutes?

Dr. SHANNON. No, sir; but they would be very well aware of the work going on at the various other Institutes.

For example, the Allergy Institute is primarily concerned with immunological problems, such as organ rejection, and it has a major role in the development of knowledge about transplantation and the substitution of an alien kidney for the patient's own nonfunctioning kidney. The Arthritis Institute is concerned with metabolic processes resulting in end products whose accumulation produces the uremic state, and the Heart Institute with cardiovascular problems which prevent the maintenance of a normal internal body environment.

In order to be sure that no barrier does, in fact, exist—and I can give a very good example of this—there is a committee, made up of our own staff, to deal with the total problem and to advise my office on the relative emphasis that should be given to various areas to be certain that tight coupling methods exist.

Now the specific example. It is possible now to predetermine whether an organ, in transplantation, will or will not take. It is not 100 per-

cent certain, but taking matched organs for transplantation one gets results about as good as one can get with identical twins.

The problem in organ replacement is to have suitable organs available at the time transplantation is needed.

One Institute proposed a program of organ storage. Organ storage could be effective for a few hours or a few days, and hopefully for substantially longer periods of time.

The monitoring of that research, viewed from the standpoint of obtaining a desirable end organ that is functioning, can better be done by the scientists in the Heart Institute, where our expertise is. Here it becomes important to develop the equivalent of what Dr. Endicott has described as task forces—take the functionally oriented physiologists and the immunologically oriented persons working on transplantation and let them operate as a group in which one supplements the other.

Mr. SMITH. Suppose you are going to try to compare the susceptibility or incidence of cancer in a group which has had pneumonia with a group who has not. At the same time someone might want to know whether they are more susceptible to some respiratory disease. Would this be coordinated so you would be securing the information from both groups?

Dr. ENDICOTT. Yes, sir. As a matter of fact, we have had for a number of years a prospective study in a large population of veterans in which there are being simultaneously observed the incidences of all types of disease. This program was laid out jointly in the first place by the Heart Institute and the Cancer Institute, it has been jointly financed, and there has been complete teamwork of the statisticians in both institutes and other scientists in laying out and following this.

I would like to take my administrative hat off for a moment and try to think back to when I used to be a laboratory man.

To me the great attraction of being at the NIH as a laboratory man was the availability of so many different talents to which I could turn for help in solving a problem I was confronted with. I have always encouraged this as an administrator, formation of interorganizational teams. You would almost have to enact laws to prevent this because they find one another.

Mr. SMITH. Before you ever begin, though, is there an obstacle created by having separate institutes engaging in the study so that all the leads that you might want to develop are developed at the same time?

Dr. ENDICOTT. Yes, sir; there are difficulties, as I am sure you know, in working across organizational lines.

In a place as large as the NIH there is even the factor of distance between one laboratory and another. It would be easier sometimes if things were different, but from a standpoint of management, in order to have effective management one man can look after only a certain number and one ends up inevitably, then, in having to create some kind of hierarchical structure for a community with 10,000 individuals. No matter how you organize one runs into need at times to cross organizational lines.

INCIDENCE OF CANCER IN DIFFERENT CITIES AND COUNTRIES

Mr. SMITH. You mentioned the statistics on the incidence of cancer in different cities. Do you have a table on that?

Dr. ENDICOTT. I would be happy to supply the information.

Mr. SMITH. Also in countries?

Dr. ENDICOTT. I want to tell you, though, that the information is not what it should be because cancer is not a reportable disease in most States and we can only estimate incidence.

We can give death rates by States. This has some weakness in it because we have such a gypsy population. The incubation period is so long in man that the fact there are more deaths relatively in urban populations may at least in part be because they move to the city in the first place to get medical care.

(The requested information follows:)

CANCER DEATHS BY GEOGRAPHICAL AREA

The following tables compare mortality rates for malignant neoplasms and various geographical configurations:

Table 1 compares crude mortality rates on metropolitan and nonmetropolitan areas as defined by Bureau of the Census.

Table 2 compares the ratio of mortality in urban and rural areas and in this table incorporated and unincorporated places of 2,500 population or more are classified as urban and the remainder as rural.

Table 3 shows the total estimated cancer deaths by State and new cancer cases by State for the year 1967.

Table 4 compares death rates from cancer in various countries.

TABLE 1.—*Crude mortality rates for malignant neoplasms in United States*

State and type of county [1]	Number of deaths	Deaths per 100,000 population							
		All sites	Digestive organs	Respiratory organs	Breast	Genital organs	Urinary organs	Leukemia and aleukemia	Other sites
United States:									
Metropolitan	175,812	154.8	52.9	24.2	14.4	21.1	7.5	7.0	27.6
Nonmetropolitan	91,815	139.6	47.1	18.5	11.5	22.4	6.5	7.3	26.3
Alabama:									
Metropolitan	1,748	117.5	32.7	18.3	10.8	23.3	4.1	5.5	22.6
Nonmetropolitan	2,043	114.9	34.2	14.0	8.4	24.0	3.3	6.3	24.6
California:									
Metropolitan	19,148	140.9	45.0	22.2	14.0	18.8	6.8	6.8	27.2
Nonmetropolitan	2,917	137.2	46.4	21.6	10.2	18.4	5.8	6.9	27.9
Illinois:									
Metropolitan	12,960	167.1	61.0	26.2	16.6	22.7	8.3	7.3	25.0
Nonmetropolitan	4,006	172.2	61.2	22.3	15.4	27.6	8.7	8.7	28.3
New York:									
Metropolitan	27,252	189.9	70.4	30.1	18.6	22.1	9.2	7.5	32.0
Nonmetropolitan	4,219	173.6	63.1	23.1	16.8	25.6	9.5	7.9	27.6
Texas:									
Metropolitan	6,685	110.1	32.5	19.3	9.0	16.6	5.0	7.3	20.4
Nonmetropolitan	4,538	129.4	41.4	20.0	9.2	21.2	5.5	7.3	24.7

[1] As used by Bureau of Census; i.e., a county or group of counties containing at least 1 city of 50,000 inhabitants or more or "twin cities" with a combined population of at least 50,000 in the 1960 census.

TABLE 2.—*Ratio: Urban/rural*[1] *mortality ratios for United States and 5 selected States*

State	All sites[2]	Digestive organs	Respiratory organs	Breast	Genital organs	Urinary organs	Leukemia and aleukemia	All other sites
United States	1.4	1.4	1.6	1.5	1.2	1.4	1.2	1.3
Alabama	1.1	1.0	1.4	1.3	1.0	.9	1.0	1.1
California	1.5	1.5	1.5	1.7	1.4	1.5	1.3	1.5
Illinois	1.4	1.4	1.7	1.5	1.2	1.5	1.0	1.2
New York	1.6	1.7	1.7	1.5	1.4	1.5	1.2	1.5
Texas	.9	.9	.9	1.0	.9	.9	1.0	.9

[1] Incorporated and unincorporated places of 2,500 population or more are classified as urban. The residual part of the county is referred to as rural.
[2] This ratio reflects number of urban cases to each rural case.

TABLE 3.—*Estimated total cancer deaths and new cancer cases by site, by State; 1967*

State	Deaths, all sites	New cases									
		All sites	Oral	Skin	Colon-rectum	Lung	Breast	Uterus	Prostate	Stomach	Leukemia
Alabama	4,400	8,500	200	2,000	750	900	900	1,100	600	300	250
Alaska	200	300	10	50	20	40	20	20	10	20	20
Arizona	2,100	4,000	60	900	400	450	400	300	300	150	150
Arkansas	3,100	6,000	90	1,300	500	550	500	550	500	250	250
California	26,500	51,000	1,400	9,200	5,900	5,400	5,800	3,400	2,700	1,800	1,700
Colorado	2,400	4,500	70	600	550	450	500	300	250	150	200
Connecticut	4,800	9,000	300	1,000	1,200	900	1,100	450	500	400	250
Delaware	800	1,500	10	350	200	200	150	100	70	50	40
District of Columbia	1,400	2,500	150	200	300	300	300	200	150	90	50
Florida	11,400	21,000	750	3,300	2,400	2,600	2,100	1,600	1,300	700	600
Georgia	5,300	10,000	300	1,900	900	1,000	1,100	1,000	750	300	300
Hawaii	700	1,500	50	100	150	150	70	80	40	100	60
Idaho	900	2,000	20	450	200	150	150	100	150	40	80
Illinois	18,500	35,000	900	4,700	5,000	3,600	4,300	2,800	1,900	1,200	1,000
Indiana	7,800	15,000	400	2,600	2,000	1,500	1,500	1,400	850	400	450
Iowa	4,800	9,000	150	1,600	1,300	850	1,000	550	700	250	350
Kansas	3,500	6,500	150	1,400	900	650	700	600	450	200	250
Kentucky	4,800	9,500	250	1,700	1,100	950	1,000	1,000	600	300	300
Louisiana	5,000	9,500	250	2,000	950	1,100	900	850	600	400	250
Maine	1,800	3,500	70	350	500	300	400	300	200	100	100
Maryland	5,200	10,000	250	1,300	1,200	1,100	1,200	750	500	250	250
Massachusetts	9,400	18,000	500	2,300	2,700	1,700	2,200	1,200	850	600	450
Michigan	12,800	24,000	700	3,300	3,100	2,500	2,600	1,900	1,500	800	700
Minnesota	5,800	11,000	200	1,600	1,400	800	1,200	600	800	500	350
Mississippi	3,200	6,000	150	1,100	600	650	500	700	500	250	250
Missouri	8,100	15,000	400	2,200	2,000	1,600	1,600	1,100	1,000	450	500
Montana	1,000	2,000	30	200	250	150	200	100	150	50	80
Nebraska	2,400	4,500	60	650	700	400	500	300	350	150	200
Nevada	500	900	20	150	100	80	100	60	50	30	30
New Hampshire	1,200	2,500	50	400	300	250	250	150	150	80	80
New Jersey	12,400	23,000	600	2,900	3,500	2,400	2,900	1,500	1,000	800	650
New Mexico	900	2,000	40	350	150	150	200	200	90	80	60
New York	33,700	64,000	1,600	7,800	9,200	6,300	7,900	4,000	2,900	2,400	1,700
North Carolina	5,600	11,000	350	1,700	1,000	1,000	1,200	1,100	700	300	400
North Dakota	900	1,500	20	250	150	100	200	80	150	80	70
Ohio	16,800	32,000	850	4,300	4,400	3,300	3,500	2,600	1,800	1,000	900
Oklahoma	4,100	7,500	150	1,500	800	850	700	550	550	250	250
Oregon	3,100	6,000	100	1,000	650	600	600	400	400	200	200
Pennsylvania	21,100	40,000	1,000	4,900	5,700	4,000	4,400	2,700	2,200	1,400	1,100

Rhode Island	1,700	3,000	150	550	500	300	450	150	150	100	80
South Carolina	2,800	5,500	150	1,100	500	500	550	750	350	200	200
South Dakota	1,000	2,000	30	350	250	150	250	150	200	80	100
Tennessee	5,400	10,000	300	2,500	1,000	1,100	1,000	1,000	700	300	350
Texas	13,900	27,000	750	6,200	2,600	3,000	2,500	2,100	1,600	950	1,000
Utah	1,000	2,000	30	450	200	100	250	150	150	70	80
Vermont	800	1,500	30	250	200	150	200	150	80	60	40
Virginia	5,700	11,000	300	1,700	1,100	1,200	1,100	950	700	350	350
Washington	4,600	9,000	250	850	1,000	900	950	600	600	300	350
West Virginia	2,900	5,500	100	900	650	600	450	500	350	200	150
Wisconsin	6,400	12,000	250	1,300	1,800	950	1,400	750	800	500	400
Wyoming	400	800	10	250	80	80	60	60	60	20	30
United States	305,000	580,000	15,000	90,000	73,000	59,000	64,000	44,000	34,000	20,000	18,000

NOTE.—These estimates are offered as a rough guide and should not be regarded as definitive. They are calculated according to the distribution of estimated 1967 cancer deaths by State. Expecially note that year-to-year changes may only represent improvements in the basic data.

TABLE 4.—*Cancer around the world: Age-adjusted death rates per 100,000 population for selected cancer sites for 24 countries, 1960–61*

[Figures in parentheses are order of rates within site and sex group]

	All sites		Oral		Skin		Colon and rectum		Lung		Breast, female	Uterus	Prostate	Stomach		Leukemia	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female				Male	Female	Male	Female
United States	141. (14)	107. (18)	4. 17(8)	1. 27(10)	2. 35(5)	1. 46(11)	18. 7(11)	16. 9(10)	31. 3(10)	4. 7(10)	21. 2(10)	13. 2(8)	13. 9(9)	12. 5(24)	6. 2(24)	7. 5(3)	4. 9(7)
Australia	133. (20)	96. (22)	3. 08(14)	1. 06(13)	4. 17(2)	2. 21(3)	17. 8(13)	17. 1(9)	27. 7(14)	3. 5(18)	19. 0(14)	9. 4(21)	14. 7(6)	18. 4(23)	9. 7(21)	6. 3(10)	4. 4(13)
Austria	193. (1)	134. (3)	2. 98(16)	0. 80(20)	1. 72(13)	1. 45(12)	18. 7(10)	13. 2(14)	48. 9(4)	5. 6(6)	16. 0(18)	20. 4(2)	13. 4(11)	45. 6(3)	26. 5(3)	6. 2(12)	4. 1(18)
Belgium	169. (5)	122. (6)	3. 01(15)	0. 79(21)	1. 47(19)	1. 16(18)	21. 7(4)	18. 3(5)	37. 9(6)	3. 9(13)	20. 3(11)	13. 9(6)	14. 2(7)	31. 4(7)	18. 1(7)	6. 6(7)	4. 2(17)
Canada	137. (16)	110. (13)	4. 16(9)	1. 29(8)	1. 75(12)	1. 24(15)	20. 4(6)	19. 8(3)	25. 4(16)	3. 6(17)	23. 1(6)	11. 3(16)	13. 4(10)	19. 5(21)	9. 6(22)	6. 5(9)	4. 5(11)
Chile	156. (12)	145. (1)	2. 00(20)	1. 10(12)	0. 82(24)	0. 86(23)	5. 8(24)	7. 4(23)	13. 6(21)	5. 0(9)	9. 7(23)	20. 6(1)	9. 7(19)	71. 0(1)	45. 8(1)	3. 7(23)	3. 4(21)
Denmark	157. (11)	140. (2)	2. 08(19)	0. 91(15)	1. 79(11)	1. 95(5)	24. 7(2)	20. 5(2)	29. 8(12)	5. 5(7)	23. 7(3)	19. 3(3)	13. 9(8)	26. 0(16)	16. 3(14)	8. 2(2)	5. 2(5)
England and Wales	175. (4)	113. (10)	3. 58(11)	1. 57(5)	1. 47(20)	1. 14(19)	22. 0(3)	17. 9(7)	62. 2(2)	8. 1(2)	23. 5(4)	10. 6(17)	11. 9(15)	25. 4(17)	13. 3(19)	5. 6(20)	3. 9(19)
Finland	187. (3)	110. (14)	3. 51(12)	1. 50(6)	2. 05(8)	1. 09(21)	9. 8(21)	9. 5(21)	56. 0(3)	3. 3(21)	13. 3(21)	11. 3(15)	11. 3(18)	45. 2(4)	26. 1(4)	6. 2(11)	4. 8(8)
France	168. (6)	105. (19)	8. 32(1)	0. 72(22)	1. 85(10)	1. 60(8)	19. 0(9)	14. 9(12)	22. 2(17)	3. 4(20)	15. 4(19)	12. 5(12)	15. 3(4)	25. 4(18)	12. 7(20)	6. 2(14)	4. 4(12)
Germany (Federal Republic of)	163. (8)	126. (4)	1. 70(22)	0. 62(23)	1. 65(14)	1. 47(10)	15. 6(16)	11. 9(17)	34. 7(8)	4. 5(11)	16. 2(17)	12. 6(11)	11. 7(16)	40. 0(5)	23. 2(5)	6. 0(17)	4. 4(14)
Ireland	133. (19)	109. (15)	5. 44(4)	1. 65(3)	3. 04(3)	1. 79(6)	19. 0(8)	17. 6(8)	26. 1(15)	5. 8(5)	19. 2(13)	7. 7(23)	9. 6(21)	23. 8(19)	16. 7(11)	5. 7(19)	3. 3(22)
Israel	121. (23)	115. (9)	1. 85(21)	0. 83(18)	1. 42(21)	1. 68(7)	9. 8(22)	9. 0(22)	19. 1(19)	6. 6(3)	21. 5(8)	5. 7(24)	8. 1(23)	22. 3(20)	15. 0(17)	9. 3(1)	5. 4(1)
Italy	139. (15)	98. (21)	5. 40(5)	0. 92(14)	1. 52(17)	1. 13(20)	12. 1(19)	10. 1(20)	21. 5(18)	3. 9(14)	14. 5(20)	13. 2(9)	8. 4(22)	34. 6(6)	18. 5(6)	5. 9(18)	4. 3(16)
Japan	135. (18)	96. (23)	1. 32(24)	0. 59(24)	0. 83(23)	0. 65(24)	7. 1(23)	6. 3(24)	10. 0(23)	3. 7(16)	3. 8(24)	15. 5(4)	1. 4(24)	69. 5(2)	36. 8(2)	3. 4(24)	2. 6(24)
Netherlands	160. (10)	119. (7)	1. 68(23)	0. 83(17)	1. 59(15)	1. 19(17)	16. 7(14)	15. 7(11)	42. 3(5)	3. 4(19)	24. 2(1)	10. 4(18)	13. 3(12)	31. 1(9)	16. 5(12)	6. 6(8)	5. 0(6)
New Zealand	136. (17)	108. (17)	3. 37(13)	1. 34(7)	2. 64(4)	2. 59(1)	19. 8(7)	18. 3(6)	28. 5(13)	4. 4(12)	22. 0(7)	10. 0(19)	13. 1(13)	19. 0(22)	9. 2(23)	6. 0(16)	5. 3(3)
Northern Ireland	147. (13)	109. (16)	4. 60(7)	1. 88(1)	1. 57(16)	1. 38(13)	21. 5(5)	18. 9(4)	36. 2(7)	5. 2(8)	18. 3(15)	9. 6(20)	11. 3(17)	27. 9(13)	16. 4(13)	6. 1(15)	4. 5(10)
Norway	125. (22)	103. (20)	2. 63(17)	1. 28(9)	1. 52(18)	1. 27(14)	12. 5(18)	10. 2(19)	12. 3(22)	2. 5(23)	17. 4(16)	9. 1(22)	15. 7(3)	29. 1(11)	17. 5(9)	7. 1(5)	5. 3(4)
Portugal	104. (24)	79. (24)	4. 68(6)	1. 15(11)	1. 26(22)	1. 05(22)	10. 6(20)	10. 6(18)	8. 7(24)	2. 4(24)	11. 4(22)	14. 1(5)	9. 6(20)	31. 3(8)	17. 4(10)	4. 5(22)	3. 2(23)
Scotland	188. (2)	126. (5)	4. 12(10)	1. 83(2)	2. 16(6)	1. 53(9)	25. 6(1)	21. 5(1)	66. 1(1)	8. 7(1)	24. 2(2)	11. 9(13)	12. 1(14)	26. 8(14)	16. 1(15)	5. 2(21)	3. 6(20)
Sweden	128. (21)	110. (12)	2. 25(18)	1. 63(4)	1. 87(9)	1. 23(16)	16. 7(15)	13. 0(15)	14. 5(20)	3. 7(15)	19. 6(12)	11. 4(14)	17. 1(2)	26. 1(15)	14. 3(18)	7. 1(4)	5. 3(2)
Switzerland	162. (9)	113. (11)	6. 24(2)	0. 89(16)	2. 07(7)	1. 98(4)	18. 5(12)	12. 4(16)	30. 3(11)	3. 0(22)	21. 3(9)	12. 7(10)	14. 8(5)	30. 4(10)	17. 6(8)	6. 2(13)	4. 4(15)
Union of South Africa	165. (7)	117. (8)	5. 76(3)	0. 82(19)	4. 56(1)	2. 48(2)	15. 3(17)	13. 8(13)	32. 5(9)	6. 2(4)	23. 3(5)	13. 9(7)	19. 7(1)	28. 6(12)	15. 8(16)	7. 0(6)	4. 6(9)

RELATION OF CANCER TO DEPRESSED MENTAL STATE

Mr. SMITH. Have studies been made on the susceptibility to cancer of persons who are in a depressed mental state?

Dr. ENDICOTT. Financially depressed?

Mr. SMITH. For any cause. Something happens and they become depressed.

Dr. ENDICOTT. Mental depression. There have been a few superficial studies of this. I don't believe there is any definite association.

Mr. SMITH. Do you have a study going on this now?

Dr. ENDICOTT. Not that I am aware of.

We have a study which is an ongoing study, with those States where cancer is a reportable disease and with a number of hospitals which maintain tumor registries we receive a duplicate IBM card for every patient in these registries every year. This contains quite a lot of information and it is continually being analyzed.

If there were a high incidence of manic-depressive states in the cancer population this would emerge as part of such a study, but I am not aware of any specific study that is directed toward this.

Mr. SMITH. I have noticed in the last 3 or 4 years that many of the people I know who got cancer had within the past couple of years suffered an adverse financial jolt, lost a member of the family or something that would tend to depress one.

Dr. ENDICOTT. Within the past few days there was a newspaper report attributed to the Sloan-Kettering Institute indicating their growing conviction that cancer may be precipitated in man by any one of a variety of things that lower his resistance.

Mr. SMITH. In Business Week, March 18, I saw this table which states that there was a study made regarding the levels of tars and nicotines in cigarettes. Was this part of the study you spoke of?

Dr. ENDICOTT. We did not contribute finances to that study.

Mr. NATCHER. Mr. Hull?

CIGARETTE SMOKING AND HEALTH

Mr. HULL. I would like to address some questions to Dr. Stewart if I may.

Then I would like to ask Dr. Endicott a few questions.

On March 29, 1966, you stated, or it was stated for you, since I understand your speech was delivered by Dr. Guthrie, that one report showed the relationship of cigarette smoking to morbidity and disability. You then referred to such figures as 12 million more chronic conditions, 300,000 extraordinary attacks, more than 1 million extra cases of peptic ulcers, et cetera.

Your speech then stated that:

> We cannot say with certainty how much of this represents a cause and effect relationship subject to reduction by reducing cigarette smoking, but the probability is its reduction would be tremendous.

That is on page 2.

I think this particular section of it, Mr. Chairman, is misleading and is a distortion because it brings in several areas so I would like to read it:

These figures suggest you are paying dearly for the cigarette habit, not only in terms of lives prematurely lost but also in terms of human suffering, medical bills in the nation's economy. Emphysema has become second only to heart disease as the cause of disability. The Social Security Administration pays more than $60 million a year to men disabled by emphysema. Perhaps when the figures for work loss days are available we will be able to estimate the annual cost to the nation in lost services and earnings of men and women killed and disabled prematurely by cigarettes. It could run into billions of dollars.

Then it continues:

Thus the mounting evidence against cigarettes would appear to be indisputable.

Don't you think that is rather misleading to one listening to it, unless emphysema is caused by smoking?

Dr. STEWART. Emphysema is a large cause of disability in the country.

Mr. HULL. I am talking about tieing it into cigarette smoking.

Dr. STEWART. As I said the other day, and as Dr. Endicott said, the cause and effect relationship between cigarette smoking and lung cancer is fairly well established, but the association of cigarette smoking with cardiovascular disease and pulmonary disease is there.

The implications are that cigarette smoking is a contributing factor to the disability and mortality of cardiovascular disease and respiratory disease.

The evidence is in that direction. It is not as strong as the evidence on the association of cigarette smoking and lung cancer at the present time.

The implication here is that if cigarette smoking declined in the country not only would lung cancer deaths decline but that other diseases which are associated with it would decline, too.

Mr. HULL. Then in your speech given March 20, 1966, you said that the report would soon be published. Has it been?

Dr. STEWART. No, sir.

Mr. HULL. What happened to it?

Dr. STEWART. I think it is in the works and being published.

Mr. HULL. I assume that showed statistical associations?

Dr. STEWART. That is right.

Mr. HULL. Don't you agree that statistical associations don't amount to proof of cause and effect?

Dr. STEWART. Given a single instance of statistical association, or a few instances of statistical association, I think it would be impossible to say cause and effect.

Given a constant association over many studies and many areas, and association always being in that one direction, the more that this occurs the more possibility there is that there is cause and effect.

If there were not an association one would expect over a certain number of studies to have the association in the other direction.

The probability of one study going the other way or not is like flipping a coin, it is 50–50. Given 20 or 25 studies one would expect, if there was no association, that the studies would show it.

Mr. HULL. Have you any other evidence?

Dr. STEWART. As far as cardiovascular disease is concerned it is based on the statistical analysis of data, with the exception of the disease that Dr. Endicott mentioned, Berger's disease, and with some

evidence that cigarette smoking will alter the blood flow of the individual.

Mr. HULL. Would you also agree that most of the so-called extra cases you referred to are not supported by the findings of the Surgeon General's Advisory Committee?

Dr. STEWART. No, I would not agree. I think the Surgeon General's Advisory Committee on Smoking and Health clearly pointed out that these associations were quite strong, and while they were not willing to go into absolute cause and effect on some of these diseases they felt that the association was strong enough that there was an increased risk through cigarette smoking.

SOURCE OF STATISTICS ON CIGARETTE SMOKING RELATED TO HEALTH

Mr. HULL. This question perhaps has been asked before, but how do you find out? Where do you get your statistics on people who have had cancer through smoking? Where do you find out about these people who are supposed to have died from lung cancer caused by smoking?

Dr. STEWART. Generally you find that where there are sufficient population groups where there are records available, the one that the late Dr. Harold Dorn used in so many of the studies on lung cancer and smoking was the veteran population of this country where there are records, male populations and records over a long period of time.

Mr. HULL. Just veterans?

Dr. STEWART. No, there are an awful lot of veterans, males.

Mr. HULL. I know there is an awful lot of people with cancer.

Dr. STEWART. They have illness records. There also have been studies in population groups in this country and in other countries which show the same relationship of cigarette smoking to lung cancers.

Mr. HULL. I am curious to know how you find out about the smokers, where you get your statistics whether they smoked one pack, two packs.

Dr. STEWART. You get that by asking them.

Mr. HULL. After he is dead.

Dr. STEWART. No, this was a prospective study.

Mr. HULL. That you thought he was going to die?

Dr. STEWART. Everybody is going to die eventually.

Mr. HULL. I wondered how you come to this conclusion.

Dr. STEWART. You take a population group and characterize the population group, including smoking habits, and you wait over a length of time and there are a certain number of deaths which occur.

Mr. HULL. Do you check back to see what they die of?

Dr. STEWART. We find out what they die from, yes. The prospective study is a standard epidemiological tool used in many efforts.

Dr. ENDICOTT. May I comment?

Mr. HULL. Yes.

Dr. ENDICOTT. In general, there are two techniques for making statistical studies of a type of cancer. One is to select a population that you know will be followed and records will be made of the occurrence of disease and the cause of death. You will assemble the necessary background information on this whole population at the beginning of the study, as Dr. Stewart said, and then you just have to wait and observe the occurrence of the cancer in question in the two populations.

Mr. HULL. You have a case history on these?

Dr. ENDICOTT. That is right, depending on the nature of the information that can be obtained by a questionnaire. In some instances it requires an interview, in other instances it requires physical or laboratory examination. It depends on what you are trying to associate.

Then you follow the population in terms of records that are generated out of some system.

The other basic approach is to go to a hospital or to a group of hospitals and get the case records from the hospital of the patients who have died of that particular form of cancer and examine the history and physical examination, the laboratory records, in retrospect to see what you can uncover from those records as to some common factor in many cases.

Those are the two basic approaches and both have been used rather extensively one place or another, one time or another, in the lung cancer and cigarette studies.

ASSOCIATION OF CANCER WITH PREVIOUS SICKNESSES

Mr. HULL. In case histories some people have had sicknesses almost from birth until they die. They would be more susceptible to cancer, I suppose, than persons out in the outdoors that lead rather vigorous lives; is that true?

Dr. ENDICOTT. I do not think the association is particularly strong. In fact, I think one would assume that the person who is susceptible to many kinds of disease is less likely to get cancer because he is less likely to live long enough.

SIGNIFICANCE OF TAR AND NICOTINE FOR HUMAN HEALTH

Mr. HULL. Dr. Endicott, just how much scientific proof is there, if any, that the amount of tar and nicotine in tobacco condensate has any real significance in terms of human health?

Dr. ENDICOTT. I would like to answer this in several ways.

The amount of tar and nicotine in a cigarette may or may not relate very closely to the amount of tar and nicotine that ends up in a man's lungs because of the differences in smoking habits, the extent to which they inhale, the length they burn the cigarette. If you place a filter on a cigarette which, let's say, removes 40 percent of the tar and nicotine and then smoke five times as many, you are not getting anywhere.

What I am saying is, low tar and nicotine content of itself does not assure that you are better off, but the tar, a fraction of the smoke, certainly contains many of the chemical substances I have been talking about, and if you are aiming at reducing the amount in the smoke, clearly this is one area for a very vigorous exploration.

Mr. HULL. What studies do you rely on?

Will you furnish a list of the titles, authors, ancillaries supporting your position?

Dr. ENDICOTT. Yes.

Mr. HULL. Will you get that for the record?

Dr. ENDICOTT. I agreed to do this already.

(See page 258 for information requested.)

Mr. HULL. The Surgeon General's Committee did not believe nicotine was a health hazard. Is that right or wrong?

Dr. ENDICOTT. I do not recall exactly what they did say about nicotine as a health hazard, the Surgeon General's Committee, but nicotine is a biologically active alkaloid which is clearly capable of producing certain reactions in living systems. It is a poison. One can use it to kill with. Nicotine in high quantities is not only a health hazard, but you can kill people with it.

So I would doubt that they took a position that it had no hazards.

Dr. Stewart, would you comment on that?

Dr. STEWART. I have forgotten the exact wording the Smoking and Health Report had in it, but I believe that it said nicotine was of a lower level of health hazard than the relationship of cigarette smoking to lung cancer.

It is, as Dr. Endicott says, a biologically active substance which does have effect on the cardiovascular system. There are adaptive mechanisms in the human body for this and I think one would have to say it is potentially a hazard.

DIFFERENCE BETWEEN CANCER IN SMOKERS AND NONSMOKERS

Mr. HULL. Can you tell cancer in a smoker from cancer in a nonsmoker?

Dr. ENDICOTT. Do you mean by examination of the patient?

Mr. HULL. However you might do it, unless he told you he smoked?

Dr. ENDICOTT. The pathologists who have had the greatest experience in examining, at autopsy, patients with lung cancer have identified a series of changes which occur in tissues of the respiratory system. They find these same tissue reactions in those people who die of other causes, not cancer of the lung. So I suspect that a really experienced pathologist——

Mr. HULL. That is all you have, is it not—really experienced ones?

Dr. ENDICOTT. They are experienced, but some have concentrated in this area a great deal of effort and have collected materials from all over large areas, a number of hospitals. A man who is, as I say, very experienced could probably make a pretty intelligent guess as to whether this man was a heavy smoker or not from just looking at the lungs and respiratory tract carefully at autopsy. The experienced pathologist can probably identify those who were heavy smokers; yes.

Mr. HULL. How can you say when a smoker gets cancer that cigarette smoking really causes it?

Dr. ENDICOTT. In the individual case you cannot say this man died because he smoked cigarettes. You cannot say that for the individual case.

Mr. HULL. Are you not intimating in all of your releases and whatnot that cigarette smoking is responsible for it and yet you say you cannot say that smoking is the cause of death.

Dr. ENDICOTT. I also list a number of other factors that cause lung cancer and in the individual case ordinarily one cannot say this man died of lung cancer because he was a heavy smoker. You cannot eliminate other factors that may have played the role in this particular case. This is always true in a probability situation.

SUSPECTED CAUSES OF LUNG CANCER

Mr. HULL. How many suspected causes of lung cancer are there?

Dr. ENDICOTT. I would hate to give you a specific number of causes.

Dr. Kotin, from a standpoint of chemicals, would you care to venture a number of different chemical substances?

Dr. KOTIN. I would say on the basis of individual chemical structures of the environmental sort to which a person may be exposed, there are probably 25 to 30 chemicals purely crystalline in form which in the lungs will result in formation of cancer in the lungs.

Mr. HULL. Would there likely be some you do not even suspect right now?

Dr. KOTIN. I would almost assure you there would be some.

Mr. HULL. Could cancer be the result of a combination of causes?

Dr. KOTIN. Most probably, sir.

A SAFER CIGARETTE

Mr. HULL. On the basis of research today, and assuming there is something unsafe in tobacco, are you in a position, Dr. Endicott, to recommend a specific way to make cigarettes safer?

Dr. ENDICOTT. I certainly am not, but I am going to work as hard as I can toward that objective.

Mr. HULL. Are you engaged in trying to find a safer cigarette?

Dr. ENDICOTT. We are not at the present time doing research on the cigarette as such. We are concentrating our efforts on identifying the dangerous materials in the cigarette. It is my conviction, as I stated earlier, that one of the major ways to make the cigarette safer is to identify the materials in it which are dangerous and try to devise some way to get rid of them.

There are several approaches. One, of course, is to modify the tobacco plant itself either through selective breeding or modifying the cultivation techniques.

Another is in the manner in which the cigarette is assembled and the additives given to it.

Another is in filtration.

Another which is perhaps more remote would be the adding of something which tends to neutralize the effect of the toxic material.

All of this potentially is in the direction of a safer cigarette. In that framework, yes, sir, we are working toward a safer cigarette.

Mr. HULL. How do you propose to evaluate any cigarette produced?

Dr. ENDICOTT. We have not ourselves crossed this bridge and are not engaged in evaluating the safety of different kinds of cigarettes.

Mr. HULL. You do not have any research going at this particular time in this field?

Dr. ENDICOTT. You mean in comparing one type of cigarette with another?

Mr. HULL. Yes.

Dr. ENDICOTT. No, sir; this is not in our area of research at the present time. At least I am not aware of it.

PLAN OF ACTION ON CIGARETTE QUESTION

Mr. HULL. Do you have a specific plan of action on this cigarette business and what is it if you do have?

Dr. ENDICOTT. We have prepared—Dr. Kotin, members of the Heart Institute, and Cancer Institute staff have prepared—a plan of action, a first draft sort of thing which I am sure will require much elaborating and modification, but yes, sir, a program has been laid out.

Mr. HULL. Has there been a secret endorsement as reported by the National Observer by the National Advisory Council?

Dr. ENDICOTT. A what, sir?

Mr. HULL. Has there been a secret endorsement by the National Advisory Cancer Council?

Dr. ENDICOTT. Endorsement of what, sir?

Mr. HULL. On this program I suppose you are working on.

Dr. SHANNON. Could I comment on that?

Mr. HULL. Yes.

Dr. SHANNON. A program was proposed by each of the three operating institutes that are concerned with this problem—the Cancer Institute, the Heart Institute, and the Division of Environmental Health Sciences.

The proposal came to my office about 3 weeks ago on a short deadline. We sent it on to the Surgeon General with a note saying, "We are submitting this without prejudice. We will wish to comment on it at a later date."

Our plan is to discuss these programs with the operating divisions and what we settle on will be incorporated in our preliminary budget. At the present time there is no definitive program that has been approved, there is a series of programs that have been proposed by the three operating divisions. That is the precise situation.

This has nothing whatever to do with advisory councils. This constitutes advice from these three operational divisions to the Surgeon General, through my office, which has been sent on without comment but it will be encompassed in our considerations in April.

Mr. HULL. What secrecy, if so?

Dr. SHANNON. There is no secrecy.

Dr. ENDICOTT. This report has not been presented to the council. I think it has actually been prepared since the last meeting of the council.

The Observer article must be referring to something else. It could not very well be this.

DIVISION OF RESPONSIBILITY FOR CANCER PROGRAMS

Mr. HULL. Dr. Endicott, what division of responsibility with other groups in Public Health Service do you have?

Dr. ENDICOTT. Responsibility is widely shared, but in the cancer area there are two principal programs in the Public Health Service.

One is the National Center for Chronic Disease Control, which is the cancer control program, and the National Cancer Institute, which is in the National Institutes of Health.

So those are the two major identified cancer programs. There is important and significant work in the field of cancer carried out in many parts of the Public Health Service.

Dr. STEWART. Mr. Hull, may I say I think the Cancer Institute is charged with finding the cause and treatment of cancer and therefore heavily pursuing research avenues and research training and all the other things that go with research.

The National Center for Chronic Disease Control is charged really with what we know now how to do, and we get it out so it becomes applied to people who have cancer or in the prevention of cancer and they work mainly with communities, hospitals, and health departments in the communities.

This is an oversimplification, but it describes the areas of efforts in the Public Health Service.

Mr. HULL. What will the total cost be in all of these programs?

Dr. STEWART. Cancer programs?

Mr. HULL. And chronic and the rest of them.

Dr. STEWART. The 1967 budget for the National Center for Chronic Disease Control, which covers the whole range of chronic diseases, is $25,102,000, and the budget of the National Cancer Institute before you for 1967 is $172,455,000.

Dr. ENDICOTT. There is another program which is identified in the enabling act in the cancer area, and this is the regional medical program for heart, cancer, and stroke, but I would not venture to say which part of this is cancer.

Dr. STEWART. It is impossible to say which is heart, which is cancer, and which is stroke.

PROGRAM ON MINING AND HEALTH

Mr. HULL. What percentage of the people that work in the mines, ones that smoke and ones that do not smoke, how many of those develop lung cancer? You never hear anything about it.

Dr. ENDICOTT. I am not sure just how far our evidence goes beyond uranium miners, but there has been a long continued study of uranium miners on the Colorado Plateau with annual physical examination, and so on, and there is, of course, a history on them of the amount and duration of their smoking habits.

Mr. HULL. You never see any large black lines saying they are subject to the diseases while working in the mines. I think you devote most of your time running down the tobacco industry and they are trying to cooperate with you. But it never makes headlines.

Dr. STEWART. We have had a major effort in the uranium mines, exposure to radium and gases and the effect on causing lung cancer over 10 or 12 years' time. It has had headlines.

Mr. HULL. Is the public aware of the Service theory of the tobacco situation?

Dr. STEWART. I think they are aware of it in the sense of a press story out recently, but very aware out in the area where the mines exist. The miners are well aware of it. We have made studies of pneumoconiosis in the coal mining industry for some 30 or 40 years, and miners are well aware, and the whole area is well aware of it in coal mining districts.

NATIONAL CENTER FOR ALCOHOLISM

Mr. HULL. Do you have a program for the alcoholics and what makes them alcoholics?

Dr. STEWART. We have a National Center for Alcoholism in the National Institute of Mental Health attempting to find out.

Mr. HULL. Are you making any progress?

Dr. STEWART. Not very much progress.

Mr. HULL. I believe that is all, Mr. Chairman.

Thank you, Doctor.

Mr. NATCHER. Dr. Endicott, we want to thank you and the members of your staff for appearing before our committee at this time in behalf of your budget request for fiscal year 1968.

JUSTIFICATION MATERIAL

National Cancer Institute

Amounts available for obligation

	1967	1968
Appropriation	$175,656,000	$183,356,000
Comparative transfers within NIH	−2,763,000	
Comparative transfer to "Office of the Secretary"	−112,000	
Transferred to "Operating expenses, Public Buildings Service," General Services Administration	−13,000	
Total	172,768,000	183,356,000

Obligations by activities

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$77,550,000		$83,317,000		+$5,767,000
General research support grants		(5,793,000)		(7,110,000)		(+1,317,000)
Scientific evaluation grants		(151,000)		(151,000)		0
Specialized research centers		(12,590,000)		(12,590,000)		0
Leukemia research support		(1,500,000)		(1,500,000)		0
Life island units		(600,000)		(600,000)		0
Fellowships		4,170,000		4,326,000		+156,000
Training		11,068,000		11,350,000		+282,000
Direct operations:						
Laboratory and clinical research	502	14,776,000	515	16,065,000	+13	+1,289,000
Collaborative research and development	714	59,815,000	737	62,985,000	+23	+3,170,000
Biometry, epidemiology, and field studies	115	1,370,000	117	1,410,000	+2	+40,000
Review and approval of grants	115	2,449,000	115	2,588,000	0	+139,000
Program direction	57	1,257,000	59	1,315,000	+2	+58,000
Total obligations	1,503	172,455,000	1,543	183,356,000	+40	+10,901,000
Unobligated balance, reserve	0	313,000	0	0	0	−313,000
Total obligations and balance	1,503	172,768,000	1,543	183,356,000	+40	+10,588,000

Obligations by object

	1967 estimate	1968 estimate	Increase (+) or decrease (−)
PUBLIC HEALTH SERVICE			
Total number of permanent positions	1,421	1,461	+40
Full-time equivalent of other positions	10	15	+5
Average number of all employees	1,371	1,440	+69
11 Personnel compensation:			
Permanent positions	$12,332,000	$12,822,000	+$490,000
Positions other than permanent	75,000	75,000	0
Other personnel compensation	120,000	120,000	0
Total personnel compensation	12,527,000	13,017,000	+490,000
12 Personnel benefits	1,253,000	1,302,000	+49,000
21 Travel and transportation of persons	535,000	550,000	+15,000
22 Transportation of things	130,000	150,000	+20,000
23 Rent, communications, and utilities	400,000	400,000	0
24 Printing and reproduction	450,000	450,000	0
25 Other services	2,787,000	3,000,000	+213,000
Project contracts	47,771,000	49,827,000	+2,056,000
Payment to "National Institutes of Health management fund"	8,836,000	9,689,000	+853,000
26 Supplies and materials	2,600,000	3,000,000	+400,000
31 Equipment	1,400,000	2,000,000	+600,000
41 Grants, subsidies, and contributions	92,788,000	98,993,000	+6,205,000
Subtotal	171,477,000	182,378,000	+10,901,000
Deduct quarters and subsistence charges	10,000	10,000	------ 0
Total, Public Health Service	171,467,000	182,368,000	+10,901,000
ALLOCATION TO VETERANS' ADMINISTRATION			
Total number of permanent positions	82	82	0
Full-time equivalent of other positions	15	15	0
Average number of all employees	95	95	0
11 Personnel compensation:			
Permanent positions	$617,000	$618,000	+$1,000
Positions other than permanent	135,000	135,000	0
Other personnel compensation	1,000	1,000	0
Total personnel compensation	753,000	754,000	+1,000
12 Personnel benefits	57,000	57,000	0
21 Travel and transportation of persons	91,000	91,000	0
22 Transportation of things	2,000	2,000	0
23 Rent, communications, and utilities	1,000	1,000	0
25 Other services	6,000	6,000	0
26 Supplies and materials	31,000	31,000	0
31 Equipment	47,000	46,000	−1,000
Total, Veterans' Administration	988,000	988,000	0
Total obligations by object	172,455,000	183,356,000	+10,901,000

Summary of changes

1967 enacted appropriation	$175,656,000
Unobligated balance, reserve	−313,000
Comparative transfers within NIH accounts	−2,763,000
Comparative transfer to "Office of the Secretary, salaries and expenses"	−112,000
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (space rental)	−13,000
1967 total estimated obligations	172,445,000
1968 estimated obligations	183,356,000
Total change	+10,901,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in:				
1. Annualization of new positions authorized in 1967				$98,000
2. Annualization of wage board salary increases				10,000
Subtotal, built-in increases				108,000
B. Program:				
1. Research grants		$77,550,000		5,767,000
2. Fellowships		4,170,000		156,000
3. Training		11,068,000		282,000
4. Laboratory and clinical research	502	8,405,000	13	629,000
5. Collaborative research and development	714	58,846,000	23	3,053,000
6. Biometry, epidemiology, and field studies	115	1,214,000	2	25,000
7. Review and approval of grants	155	1,497,000		44,000
8. Program direction	57	869,000	2	32,000
Subtotal, program increases			40	9,988,000
C. Payment to National Institutes of Health management fund for centrally furnished services:				
1. Laboratory and clinical research		6,371,000		622,000
2. Collaborative research and development		969,000		106,000
3. Biometry, epidemiology, and field studies		156,000		11,000
4. Review and approval of grants		952,000		97,000
5. Program direction		388,000		17,000
Subtotal, management fund increases				853,000
Gross increases			40	10,949,000
DECREASES				
A. 1 less day of pay (261 days in 1967; 260 days in 1968)				−48,000
Total net changes requested			+40	+10,901,000

EXPLANATION OF CHANGES

Research grants.—The program increase of $5,767,000 will provide $4,450,000 for regular program grants and $1,317,000 for general research support grants.

Fellowships.—The program increase of $156,000 will provide $31,000 for postdoctoral fellowships, $120,000 for special fellowships, and $135,000 for research career development awards. These increases are offset by a decrease of $130,000 in career awards which are being phased out.

Training.—The program increase of $282,000 is requested to strengthen the graduate training program.

Laboratory and clinical research.—The program increase of $629,000 is requested to support 13 new positions and the cost of setting up operating laboratories when the new building is completed. Primary emphasis will be on expansion of research in cell biology, developmental biology and immunology.

Collaborative research and development.—The program increase of $3,053,000 is requested for support of 23 new positions and expanded contract programs in the areas of carcinogenesis, viral oncology, clinical trials, and experimental therapeutics, and would also provide increases for the special virus-leukemia program and breast cancer activities. Positions and funds are also included for the move to the new cancer building and supporting services in the new building. Recently established task forces on breast cancer, solid tumors, and lung cancer will continue in operations in 1968.

Biometry, epidemiology and field studies.—The program increase of two positions and $25,000 would be used to initiate a 10 city survey of the incidence, prevalence and mortality of cancer in the United States.

Review and approval of grants.—The program increase of $44,000 will support the added cost of reviewing the increased grant and contract programs.

Program direction.—The program increase of 2 positions and $32,000 is requested to augment the planning, programming and budgeting and program analysis functions.

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".

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;"

Explanation of transfers

	1967 estimate	Purpose
Comparative transfer to "Office of the Secretary, DHEW, salaries and expenses."	−$112,000	Indirect cost analysis.
Comparative transfers within NIH	−2,763,000	Redistribution of the NIH management fund.
Transferred to "Operating expenses, Public Buildings Service," General Services Administration.	−13,000	Transfer of rental costs to General Services Administration.

RESEARCH GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$56,916,000	$61,366,000	+$4,450,000
Special programs	20,634,000	21,951,000	+1,317,000
Total research grants	77,550,000	83,317,000	+5,767,000

Introduction

Research grant funds support activities in the cancer field within universities, hospitals, laboratories, research institutes, and other public or private nonprofit institutions. The purpose of these grants is to stimulate new investigations in fields where further exploration seems likely to be fruitful. The projects range from small, circumscribed activities to broad composite programs that integrate the research interests of many investigators in a variety of scientific disciplines. These grants make possible complex clinical research which would otherwise not be accomplished for many years.

Program plans in 1967

Grant-supported research will continue to place emphasis on studies of the biology and chemistry of growth, reproduction and differentiation of the normal malignant cell. It will include, also, extensive studies on various kinds of cancer in laboratory animals, along with individual studies of the cancer patient, and cancer in populations.

The Institute will support projects aimed at developing methods for identification of carcinogenic agents and hazards in man's total environment; atmosphere, water, food, drugs, tobacco, other natural products, occupation, radiation and infectious agents. Studies aimed at the viral etiology of malignant diseases will be emphasized. Grants will also support studies of various forms of therapy, especially chemotherapy and related pharmacologic studies of neoplastic diseases. Other studies will be devoted to radiobiology, especially the application of tools

and techniques from experimental radiobiology to radiation therapy so that cancer cells can be made more sensitive to radiation and normal cells less affected thereby increasing the effectiveness of radiation therapy. Since there is increasing evidence that cancer is essentially a cell disease, research efforts will be broadened to cover both extrinsic and intrinsic factors which might be involved in the cancerous change. The areas to receive expanded support will include cell biology, carcinogenesis and clinical research.

The programmed chemotherapy grant program will continue to provide support for clinical studies performed under extablished protocols to evaluate new agents for use as therapeutic materials for various types of malignancies.

Approximately 35 leukemia research support centers will be funded in 1967. These centers will continue to study new research therapy techniques involving new drugs and blood platelet transfusions to patients on both an outpatient and inpatient basis.

Cancer Institute grants now support 20 specialized research centers. These centers are now beginning to emphasize research on host defense mechanisms against tumors, the effect of cytotoxic drugs on immune responses, and attempts to define more precisely the mechanism of the action of anticancer agents. Furthermore, studies of radiation biology, physics, and nuclear medicine have been expanding. Much attention is being given to determinations of 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. The funds for 1967 will allow increased support for existing activities plus the inauguration of several new installations. The specialized research centers item also includes planning grants which support costs incurred by institutions in the development of long-term plans for cancer research, training, and clinical service. In the 1967 budget, the centers were identified as "Categorical clinical research centers" ($7,790,000) and the planning grants were identified as "Specialized research centers" ($800,000).

The $600,000 available for life islands and related reverse isolation units such as laminar flow units will be sufficient to provide continued support to the six active grants. Life islands are enclosures in which patients are kept in essentially a germ free environment. Laminar flow units also isolate the patient through devices to control the flow of air. These are of interest because cancer drug dosages can be increased to higher levels in such environments without a corresponding increase in inside reactions.

Program plans in 1968

The $40,228,000 earmarked for support of non-competing continuations projects contains an increase of $2,580,000 over the 1967 level of support, representing 15 additional grants which will have a moral commitment during 1968.

The $17,173,000 requested for competing projects includes $10,278,000 for new regular research grants, which is an increase of $3,675,000 over the 1967 level of support for new grants. This increase permits the awarding of an additional 73 new awards in 1968.

The increase in new grants is partially offset by an estimated decrease in competing continuations of $1,993,000 and 53 grants. The net figure for competing grants is therefore an increase of 20 grants and $1,682,000. The major factor in these items is the cyclical pattern of the termination and subsequent renewal of continuations. The variance can be large from one year to another. Supplemental grants are expected to require some $188,000 more in 1968. The overall net increase in 1968 over 1967 for regular project grants is estimated at 35 grants and $4,450,000.

High priority will be given to support of research in the following areas: 1) studies aimed at determining the relationship between man's environment and his liability to malignant diesases, 2) research in the field of clinical pharmacology with particular emphasis on early diagnosis through specialized instrumentation, 3) research aimed at the development of better forms of treatment, 4) studies of viruses and their role in causing malignant disease, and 5) research relating to the development and application of tools and techniques for experimental radiobiology and radiation therapy.

The programmed chemotherapy grant program will remain at the same level in 1968, continuing to support the efforts of study groups operating under highly developed protocols.

The specialized research centers program will continue at the same dollar level in 1968. The increase from 36 to 40 grants is possible because some recently initiated grants which required high "start up" costs will need only operating funds in 1968.

The leukemia research support centers are expected to continue at the same level in 1968 as in 1967. Pending requirements will be mainly for 27 non-competing continuations, the result of grants awarded in 1966 and 1967. In 1968 anticipated increases in the number of applications will allow greater latitude in funding selectivity. Further evidence will be accumulated regarding platelet replacement therapy and its use as an effective tool in connection with the administration of control drugs.

In 1968 the life island program is expected to continue at the same level. The techniques of reverse isolation will continue to be studied in combination with chemotherapy and radiation techniques.

Research grants program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
Cancer causation	$13,027,000	$14,202,000	+$1,175,000
Tumor growth	11,655,000	12,706,000	+1,051,000
Host-tumor relationship	2,895,000	3,156,000	+261,000
Epidemiology	1,559,000	1,699,000	+140,000
Diagnosis	1,074,000	1,171,000	+97,000
Therapy	11,644,000	12,694,000	+1,050,000
Basic research and other [1]	10,719,000	11,395,000	+676,000
Programed chemotherapy	4,343,000	4,343,000	0
Subtotal, regular program	56,916,000	61,366,000	+4,450,000
General research support grants	5,793,000	7,110,000	+1,317,000
Scientific evaluation grants	151,000	151,000	0
Specialized research centers	12,590,000	12,590,000	0
Leukemia research support centers	1,500,000	1,500,000	0
Life island units	600,000	600,000	0
Total research grants	77,550,000	83,317,000	+5,767,000

[1] Includes Sloan-Kettering single instrument grant.

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	870	$37,648,000	885	$40,228,000	+15	+$2,580,000
2. Competing projects	355	15,491,000	375	17,173,000	+20	+1,682,000
3. Supplementals	(175)	3,777,000	(180)	3,965,000	(+5)	+188,000
4. Subtotal, regular program	1,225	56,916,000	1,260	61,366,000	+35	+4,450,000
5. General research support		5,793,000		7,110,000		+1,317,000
6. Scientific evaluation		151,000		151,000		0
7. Specialized research centers		12,590,000		12,590,000		0
8. Leukemia research support centers		1,500,000		1,500,000		0
9. Life island units		600,000		600,000		0
10. Total research grants		77,550,000		83,317,000		+5,767,000

Fellowships

	1967 estimate	1968 estimate	Increase or decrease
Total fellowships	$4,170,000	$4,326,000	+$156,000

Introduction

The purpose of the fellowships program is to increase the supply of investigators and teachers trained in basic and clinical sciences related to the field of cancer research. The program provides research training to individuals whose career development extends from the immediate post doctoral period through the advanced stages of scientific attainment. Post doctoral awards are made to qualified individuals with doctorate degrees but with little or no previous experience. Special fellowships are awarded to qualified individuals who have had at least three years post doctoral research or professional experiences.

This budget activity also supports two other types of awards made to institutions for the purpose of increasing the number of stable, full time career opportunities for scientists of high potential and capability in disciplines important to cancer research. The Research Career Development awards support investigators who require 5 to 10 years experience in order to improve their research skills and to develop a capability for independent investigation. Research career awards are made to established investigators of high quality for the duration of their research careers.

Program plans in 1967

In 1967 the number of awards in both the Postdoctoral and Special categories will remain fairly stable. As in the past, the Institute will select qualified individuals for specialized research training in such fields as immunology, biochemistry, cytogenetics, endocrinology, virology, and pathology. Continued emphasis will be given to encouraging interest and increasing training in the critical shortage areas of radiation therapy, surgery, hemotology, and clinical pharmocology and toxicology.

As a result of the NIH decision not to make additional Research Career awards, Research Career Development awards have and will continue to take on increased significance which will be reflected in modest but progressive increases in the number of awards made.

Program plans in 1968

With the requested increase of $156,000, the Institute plans to add a net of 8 special fellowships for candidates interested in the research aspects of radiation, therapy, surgery, hemotology, and clinical pharmacology and toxicology. The remainder will be applied to the moderately expanding development program and will be sufficient for funding a net increase of 13 Research Career Development awards. These increases are offset by decreases of 5 postdoctoral and 6 career awards.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	123	$1,980,000	185	$2,970,000	+62	+$990,000
(b) Competing	48	925,000	31	283,000	−53	−642,000
2. Supplementals	0	0	0	0	0	0
3. New awards	146	1,265,000	147	1,073,000	+1	−192,000
4. Total fellowships	353	4,170,000	363	4,326,000	+10	+156,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Postdoctoral	138	$890,000	133	$921,000	−5	+31,000
2. Special	97	955,000	105	1,075,000	+8	+120,000
3. Research career:						
(a) Career	18	477,000	12	347,000	−6	−130,000
(b) Development	100	1,848,000	113	1,983,000	+13	+135,000
4. Total fellowships	353	4,170,000	363	4,326,000	+10	+156,000

TRAINING GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Total training grants	$11,068,000	$11,350,000	+$282,000

Introduction

Graduate research training grants are made to institutions to help provide an adequate supply of competent research manpower, and to alleviate critical shortages of professional personnel in selected areas affecting the combination of research, teaching, and service. In addition to underwriting expenses for equipment, supplies, and training staff, these grants may provide stipends for individuals in training for a wide diversity of fields related to cancer research. Clinical cancer training grants assist qualified institutions in improving and expanding training in the prevention, diagnosis, treatment, rehabilitation, and public health aspects of cancer. The threefold purpose of these grants is to encourage institutions to: 1) upgrade the quality of cancer instruction offered to undergraduate and graduate medical, dental, and public health students and to interns, residents, clinical fellows, and practitioners; 2) broaden the scope and content of current cancer teaching; and, 3) undertake innovations in methods for teaching the clinical and public health aspects of comprehensive cancer management.

Program plans in 1967

Approximately 157 programs will be supported during the current year. Continued emphasis will be given to training in clinical pharmacology and chemotherapy, including the trial of new chemotherapeutic agents and new dosages, development of evaluative criteria for small effects and objective assay of the response of cancer cells to agents. Emphasis will be placed on establishing additional programs of clinical research training as well as conventional graduate programs in disciplines where cancer researchers are in short supply. Also, programming efforts will be strengthened in: 1) radiobiology and radiotherapy, 2) experimental surgery and physiology, 3) virology, and 4) nuclear medicine.

Program plans in 1968

The 1968 request includes the support of 8 new programs as compared with 17 in 1967 for a net decrease of 9 grants. Continuing programs being renewed in 1968 will increase by 17. This allows a net increase of 9 cancer clinical training grants offset by a decrease of 1 graduate grant. However, the entire $282,000 increase will be used to support the increased cost of established graduate programs. The renewal cost of the existing but relatively new cancer clinical training programs will be reduced to allow for the net increase of 9 grants.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	125	$8,399,000	139	$9,591,000	+14	+$1,192,000
(b) Competing	15	939,000	18	970,000	+3	+31,000
2. Supplementals	(12)	600,000	(6)	139,000	(−6)	−461,000
3. New program	17	1,130,000	8	650,000	−9	−480,000
4. Total training grants	157	11,068,000	165	11,350,000	+8	+282,000

Training grants (by program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Graduate	82	$5,598,000	81	$5,880,000	−1	+$282,000
2. Cancer clinical training	75	5,470,000	84	5,470,000	+9	0
3. Total training grants	157	11,068,000	165	11,350,000	+8	+282,000

Laboratory and Clinical Research

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	502	$5,005,000	515	$5,181,000	+13	+$176,000
Other expenses		9,771,000		10,884,000		+1,113,000
Total	502	14,776,000	515	16,065,000	+13	+1,289,000

Introduction

The research programs within this activity are directed toward providing a basic understanding of the cancer process. Such research is broadly based in order to achieve adequate coverage and integration of knowledge applicable to the problems of cancer. Emphasis, however, is placed on certain areas of research which appear to have special relevance or which require greater attention because of the particular nature of the problem involved. It is recognized that this type of probing research will constantly change to take advantage of new information that may be of use to any of the research areas involved, or that may be exploitable for possible practical control of cancer in man.

Since cancer attacks all part of the body and all body systems with many variations, it must be studied from many scientific points of view. Laboratory and Clinical Research, therefore, covers a range extending from the molecular level to the clinical level, reflected by the internal organization according to traditional disciplines—i.e. biochemistry, biology, physiology, pathology, etc.

Program plans in 1967

Scientists in these laboratories are building up the knowledge of body chemistry, of cell growth and reproduction, of host resistance to tumors and how the body regulates cell growth. Through this knowledge gradually acquired will come answers that will eventually help to prevent or treat cancer. Animal model systems developed in these intramural labs are the foundation for the more direct attack on cancer carried on as collaborative programs.

Currently under increasing attention are immunologic factors possibly important in the causation and course of cancer, and perhaps exploitable in its control. Some evidence to date has suggested certain immunologic aberrations may be conducive to the beginning and development of the cancer process. Possibly of greater importance is other evidence indicating that the immunologic defenses normally operate to control the disease. Although it is not known how frequently a malignant tumor is spontaneously controlled by the immunologic defenses of the body, it is known from animal studies that the development and transplantability of some viral-induced cancers can be prevented by immunologic means. While it may be expected that immunologic modalities in the future will be found to be therapeutically useful in the treatment of human cancer, there is insufficient evidence to warrant undertaking therapeutic trials in man at this time.

Program plans in 1968

The established laboratories organized on a discipline basis will continue to pursue new leads, as knowledge in their disciplines provides new opportunities.

An urgent need exists for a substantial amount of research assessing the degree to which immunologic factors actually operate in the spontaneous control of human cancer. Expansion of research facilities and capabilities to accomplish this is incorporated into the program plans for the immediate future.

Malignant transformation of the cell, the fundamental change by which a cell becomes cancerous, will receive greater emphasis. While it is known that a number of environmental agents are carcinogenic, the specific effects on the cell that cause its transition from a normal to a malignant cell need to be clarified. Extension of ongoing research is required to determine whether other agents, such as radiation and chemicals, can cause malignant transformation of a cell by themselves or whether the presence of a virus is also necessary.

Further expansion of research in cell biology and developmental biology is projected to acquire new knowledge on the natural controls involved in the normal differentiation and maturation of cells during the period of embryonic development. Little success has been achieved in the past in mounting and maintaining a continued research program due in part to the shortage of scien-

tists trained in these areas. Efforts are being directed toward bringing into this research area scientists who have been trained in the technologies that have developed out of nucleic acid and protein research.

The program increase $629,000 and 13 positions for 1968 would permit pursuit of ongoing research and the extension and undertaking of the programs described above. Included in this program increase are funds for the move into the new building and for the renovation of laboratory space thereby made available for improved clinical research in the Clinical Center.

An increase of $38,000 is requested for mandatory items such as annualization of positions new in 1967 and annualization of wage-board pay increase in 1967, offset by one less day of pay in 1968 and non-recurring items. There are also increases of $622,000 for centrally furnished services from the "National Institutes of Health Management Fund."

COLLABORATIVE RESEARCH AND DEVELOPMENT

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	714	$6,022,000	737	$6,333,000	+23	+$311,000
Other expenses		53,793,000		56,652,000		+2,859,000
Total	714	59,815,000	737	62,985,000	+23	+3,170,000

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 following table indicates level of support by these major program areas:

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Etiology	272	$28,715,000	280	$30,724,000	+8	+2,009,000
Cancer therapy	380	29,042,000	390	29,686,000	+10	+644,000
Supporting services	62	1,089,000	67	1,500,000	+5	+411,000
National Institutes of Health management fund		969,000		1,075,000		+106,000
Total, collaborative studies	714	59,815,000	737	62,985,000	+23	+3,170,000

ETIOLOGY

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Total	272	$28,715,000	280	$30,724,000	+8	+$2,009,000
Office of the Scientific Director	43	801,000	43	801,000	0	0
Carcinogenesis	85	1,336,000	87	1,687,000	+2	+351,000
Viral oncology	88	1,215,000	94	1,613,000	+6	+398,000
Etiology contracts		10,717,000		11,417,000		+700,000
Special virus-leukemia	56	14,646,000	56	15,206,000	0	+560,000

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 study of defined human and animal populations, to studies under laboratory conditions of the fundamental aspects of growth and 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 his environment. The Demography programs (described in detail under "Biometry, Epidemiology and Field Studies") are designed to analyze defined populations having unusual risks to specific cancers or known exposure to high risk environments, in order 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 1967

Carcinogenesis.—A major concern of the organizational groups funded under this budget activity continues to be an approach to cancer causation through a study of the role of environmental factors. This approach depends upon the characterization of the occurrence and behavior of cancers by specific sites in human populations. The role of environment is investigated by studying cancer characteristics in domestic and foreign populations and in populations migrating between countries with differing environmental conditions.

Collaborative studies, supported by contracts, are being continued in addition to in-house activities aimed principally at the identification and characterization of known and suspected chemical carcinogens, especially those commonly occurring in the human environment. Efforts to improve bioassay methods employed in the identification and characterization of chemical carcinogens with the aim of improving the relevance of animal data to the human situation, and the study of effects of known and potential carcinogens at the cytologic and genetic levels is also a major part of the current program. Predominant among these activities are the multi-project agreements with the Atomic Energy Commission at Oak Ridge, the Chicago Medical School, and, more recently, New York University.

The activities which emphasize the fundamental nature of the interaction of carcinogenic agents with living systems in the induction of cancer at the host, tissue, cellular, and molecular levels, are progressing in a most satisfactory manner. These studies endeavor to understand the normal molecular functioning of cells and how these processes are altered by agents which induce cancer. They include the effects of cancer-causing viruses, chemicals, and radiation on the genetic composition, and on the transmission and translation of genetic information within the cell. Attempts are made to delineate the molecular mechanism by which normal cells are converted to cancer cells. In addition, the roles of

certain inheritable characteristics in humans are being determined in relation to their resistance or susceptibility to various forms of cancer in particular leukemia, cancer of the lung, and cancer of the breast.

Viral Oncology and Special Virus-Leukemia

The three branches within the Viral Oncology Area are staffed with specialists in the scientific disciplines specifically needed to conduct comprehensive basic research on all of the aspects of the virus-cancer relationship, and to manage the related programs of developmental and applied research that are essential to the achievement of the goals of the National Cancer Institute with respect to viral oncology.

The National Cancer Institute's activities in viral oncology may be divided into several major programs, including the Special Virus-Leukemia Program which is a program of experimental work on "fluid" tumors, the program of research on viruses in the induction of "solid" tumors, and the program to devise and develop physical and other resources to facilitate expanded efforts in viral oncology.

This year efforts are being continued in the Special Virus-Leukemia Program to produce, concentrate, and purify viruses derived from human leukemia material in order to conduct animal experiments in leukemogenesis. The acquisition of fresh material from different types of human leukemia and lymphoma has been increased and considerable progress is being made in the development of a computer storage and retrieval system for data obtained on these patients.

The apparent persistent and predominant association of a herpes-like virus in tissue cultures begun from buffy coat or tissue cells of 39 patients from 4 different countries, demands that additional intensive studies be conducted to determine possible etiological significance of this virus type to human leukemia and lymphoma. In particular, within 1967 approximately ten of these cell lines will be selected for propagation in kilogram quantities. The immediate objective of this study is to prepare virus concentrates from these extracted cells, which will then be used in studies to determine their biological, chemical, and physical characteristics. It is anticipated that such materials will permit necessary seroepidemiological surveys designed to determine the comparative distribution of this virus and/or virus antigen material within normal and diseased population groups.

In other programs concerned with viral oncology, scientists continue development of activities designed to study the action of DNA viruses in the induction of "solid" tumors of animals as well as their possible role in the causation of some cancers of man. These viruses, producing tumors in solid tissues as opposed to tissues that produce circulating cells in the blood and lymph, require studies on a broad collaborative scale analogous to those on the leukemia-causing RNA viruses now underway in the Special Virus-Leukemia Program. Plans for this program were formulated in discussions at several meetings of the National Cancer Institute's scientists with the nation's most eminent researchers concerned with the role of DNA viruses in tumor induction. It is the concensus of these scientists and researchers that laboratory techniques and seroepidemiologic methods now available are adequate to insure significant progress in this area.

Electron microscopy also continues to be a major approach to the virus-cancer problem. The electron microscopy staff is playing a key role both in the advancement of basic knowledge and in guiding and monitoring the search for and study of viruses associated with leukemia and other cancers of humans.

Program plans in 1968

Carcinogenesis.—During 1968 a net increase of $651,000 including $300,000 for contracts and 2 positions is requested to expand and initiate studies concerned with: 1) mechanisms of carcinogenesis at the molecular level; 2) the association of carcinogenesis and teratogenesis as well as concordances of cancer with other systemic non-neoplastic diseases; and 3) the role of the organs and tissues responsible for the formation of various blood cells and fractions involved in the immunological response of a host to carcinogenesis. Implementation of these activities will take place within the new Cancer Building to be completed early in 1968.

Viral Oncology and Special Virus-Leukemia.—A net increase of $798,000 including $400,000 for contracts and 6 positions is requested to support an expansion of the electron microscopy effort necessary to meet the increasing demands of the Special Program and others in the field of viral oncology, as well as launch the

first major phase of the solid tumor-DNA program, within the new cancer facility.

A net increase of $560,000 is requested to permit the expansion of efforts in those areas of the Special Virus-Leukemia Program where progress has been made as anticipated in the 5 year projection of activities. Studies will be launched to determine the extent to which viruses of the type now being frequently detected in human leukemia and lymphoma are associated with these human diseases in general, and whether they are causally related thereto. An important part of the proof of the latter will be the reduction of the diseases in vaccinated populations, when the totality of evidence indicates that such vaccination studies are justified. Toward this future eventuality developmental research will be launched on the practical large-scale production of viral antigen, and the devising of stable and efficient vaccines, using one or more of the viruses from human leukemia and lymphoma now available. These activities are critical to the continued advancement of the program.

CANCER THERAPY

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Total	380	$29,042,000	390	$29,686,000	+10	+$644,000
Office of the Scientific Director	82	2,000,000	82	2,000,000	0	0
Clinical trials	82	733,000	86	833,000	+4	+100,000
Experimental therapeutics	42	497,000	48	728,000	+6	+231,000
Cancer Chemotherapy National Service Center	64	718,000	64	718,000	0	0
Therapy contracts	82	20,592,000	82	20,592,000	0	0
Breast cancer activities	12	2,487,000	12	2,800,000	0	+313,000
Special virus-leukemia	16	2,015,000	16	2,015,000	0	0

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 the 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.

Program plans in 1967

During the past two years the cost of the Cancer Therapy Program has been reduced by the elimination of contract programs or sharp reduction in certain contracts. The program has been highly streamlined and focused into a clearly defined plan. All new projects initiated during 1967 are being funded through reduction or deletion of existing programs.

Additional research is being performed on improving drug toxicity screens, both quantitatively and qualitatively. This concerns the prediction of a safe dose of a new drug in early clinical trials and the prediction of the specific organ damage to be expected when drugs are given to patients. The relations of chemical structure of antitumor drugs to activity and safety will emerge slowly. The Institute has completed a preliminary survey of the 30 or more chemicals known to be effective in clinical cancer and is now reviewing the structural implications of the 6 most important chemical series. From this analysis will come a chemical synthesis program designed to develop the full picture of structure—activity relations which will lead to more active and less toxic drugs. Similarly, antitumor drugs obtained from natural products are being analyzed in an effort to relate activity to families or genera of plants and ultimately to chemical structure. Analysis indicates that relatively few plant species have been examined and that the animal kingdom is virtually untouched.

In the clinical trials program substantial drug effects, approaching cure, are being observed in acute leukemia, Hodgkin's disease, choriocarcinoma, Burkitt's lymphoma, testicular tumors and childhood solid tumors. These are all rapidly growing tumors. The tumors less susceptible to drugs are considerably slower in growth rates and are requiring the major clinical effort in the search for new drugs.

A Breast Cancer Task Force, constituted during 1967, is directing its activities toward a concerted effort to determine the cause of breast cancer and to determine the best therapy. The Task Force approach has been taken because of the realization that the cure rate of breast cancer has not improved significantly over the past several decades. The program includes both basic and applied research on cause, diagnosis and treatment.

The therapy efforts in the Special Virus-Leukemia Program are coordinated through the Acute Leukemia Task Force which consists of investigators in over 90 institutions participating in a major collaborative and cooperative effort. During 1967, this group continued to develop projects concerned with: 1) the intensification and expansion of research and its application to achieve the ultimate therapeutic objective of the complete destruction of all leukemia cells with tolerable toxicity for the patient, and/or the development of drugs, procedures, regimens, etc. for the prophylactic treatment of "preleukemics" and 2) providing to the Resources and Logistics Working Group tissue and plasma specimens from untreated fulminating leukemics, erythroleukemics, et al., for collection, storage, and distribution to other program segments.

Program Plans in 1968

In 1968 the renovation of laboratory space at the Baltimore Public Health Service Hospital will be completed and the existing clinical program will be expanded to form an integrated program of laboratory and clinical research on the therapy and management of cancer patients, including pharmacologic investigations of the mechanisms of action of anticancer drugs. This program is a collaborative endeavor between the Baltimore Public Health Service Hospital and the National Cancer Institute. A net increase of $100,000 and 4 positions is requested for the expanded clinical program and a net increase of $231,000 and 6 positions is requested for the new pharmacology program.

Additional research must be performed in the improvement of drug toxicity screens. Each addition to the screen will be expensive and should be made based on solid evidence that the addition supplies important information not derivable from the present two-tumor screen. Another problem of putting drugs into man safely concerns their formulation into the final preparation to be given to man. Many of the new agents are of large molecular size and poorly soluble. Research on new and safer solvents for these new materials is planned for 1968.

The use of platelets has been essential to intensive cancer therapy. At present, platelets must be used within a few hours of collection. As a result few institutions have them available. Research on freezing and prolonged storage of platelets will be fostered to remove this limitation.

In the area of breast cancer, extensive efforts will be made to identify high risk groups of women, with the aim of increasing the proportion of cases diagnosed in the potentially curable early phase of the disease. A study is to be made of the natural factors favoring control or disssemination of breast cancer, particularly hormonal factors now suspected of having special importance. There is an anticipated unobligated balance of $313,000 for this program in 1967 due to the fact that the program was not funded until late in the fiscal year. This amount is restored in 1968.

Special reports have been furnished to the Committee on the breast and solid tumor task forces. Because of the alarming increase in lung cancer the National Advisory Cancer Council recommended the creation of a lung cancer task force. This task force, like many of the others, will utilize the resources provided in collaborative programs or through grants to carry out its objectives. A chairman of this task force has been selected and the task force is expected to become more fully operational in fiscal year 1968.

SUPPORTING SERVICES

Several service type functions which benefit the whole Institute are included under the Collaborative Research and Development activity, including funding for the NCI Journal, Administrative Services, and other service functions.

In 1968, a program increase of $400,000 and 5 additional positions is requested to fund the cost of moving into the new Cancer Building and the central services required therewith.

Also requested for the total Collaborative Research and Development program is $11,000 for mandatory items such as annualization of positions new in 1967 and annualization of wage-board pay increase in 1967, offset by one less day of pay in 1968 and non-recurring items. There are also increases of $106,000 for centrally furnished services from the "National Institutes of Health Management Fund."

BIOMETRY, EPIDEMIOLOGY, AND FIELD STUDIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	115	$1,034,000	117	$1,063,000	+2	+$29,000
Other expenses		336,000		347,000		+11,000
Total	115	1,370,000	117	1,410,000	+2	+40,000

Introduction

Characterization of the occurrence and behavior of cancers by specific sites in human populations, both in the United States and abroad, and the effects of migration on these cancer patterns continues to be the major concern of 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 1967

During this year, the Epidemiology Branch plans to further augment the studies on concordances between congenital defects and cancers. The Branch is also establishing a registry of birth and death certificates for all children who die of cancer in the U.S. before 15 years of age, from 1960 on. This registry will make possible studies of the aggregation of cancer by type among sibs, twins, or geographically (by dates of birth or death). In addition, it will be possible to: 1) relate items on the birth certificate, such as maternal age or economic status, to the cause of death; and, 2) follow up groups suspected to be at unusual risk of neoplasia.

The Biometry Branch will continue its current program, with special emphasis upon the studies of cancer patterns in migrant populations. This Branch provides the biometric competence for the reporting of results emanating from experimetal cancer therapy, and therefore provides an essential ingredient in identifying those therapeutic measures which may have potential value in the treatment or control of cancer in man. Its major effort to evaluate x-ray mammography as a diagnostic tool for use in early detection of breast cancer is showing laudable promise; success will determine whether or not vast sums of money should be spent on this technique as a public health measure in cancer diagnosis.

Activities of the newly established Epidemiologic Pathology Unit in 1967 include: 1) the study of multiple primary cancers of various anatomical sites as a special etiological situation; 2) an analysis of pathology data in existing tumor registries to determine their adequacy for the types of studies envisioned; and, 3) the establishment of additional resources required to furnish needed data.

Concern with a possible relationship between cancer and selected occupations combined with the growth in number, efficiency, and reliability of hospital cancer registries, state tumor registries, and the willingness and cooperation on the part of industries made it feasible to attempt to determine the actual contribution of occupational cancer to the total cancer spectrum in the United States. Consequently, an Occupational Carcinogenesis Unit has been established this year to concern itself with the specific compilation and study of data associated with the incidence of neoplastic disease among selected occupations believed to be high risk.

Program Plans in 1968

In addition to the continuation of the above, a program increase of 2 positions and $29,000 is requested to support the first phase of the "Ten Cities Cancer Survey Program" to be conducted in relation to the 1970 decennial census.

The essential nature of the ten-cities survey to the entire biometric effort to characterize cancer incidence and behavior in the United States makes this a strategic item. Without the information to be derived from this survey the majority of other studies of cancer in human populations in the United States, during the ensuing 10-year period, will be of unknown reliability.

The planning for this activity will be performed by the Biometry Branch, but the implementation itself in 1970 will, of course, require the participation of outside groups, particularly the Bureau of the Census. The purpose of this survey is to provide baseline information about the populations of the United States for use in the evaluation and interpretation of specially collected data for a wide variety of need in the Biometry Branch programs. To the extent possible it will be planned to complement the Regional Medical Programs of the National Institutes of Health.

An increase of $4,000 is requested for mandatory items such as annualization of positions new in 1967 and annualization of wage-board pay increases in 1967 fully offset by one less day of pay in 1968 and non-recurring items. There are also increases of $11,000 for centrally furnished services from the "National Institutes of Health Management Fund."

REVIEW AND APPROVAL OF GRANTS

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	115	$1,114,000	115	$1,116,000	0	+$2,000
Other expenses	--------	1,335,000	--------	1,472,000	--------	+137,000
Total	115	2,449,000	115	2,588,000	0	+139,000

Under the Associate Director for Extramural Activities, this activity supports the administrative staff for all contract activities and both the scientific and administrative staff responsible for the review of all cancer grants. The staff obtains the necessary information about 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 applications. The program increase of $44,000 will be used entirely for the continuation of existing activities and will cover the cost of site visits, travel of new grants review committees, etc., necessitated by the increase in the number of grantees and to provide better review of grants.

Included in the $139,000 net increase is a $2,000 decrease resulting from one less day of pay in 1968 offset by annualization of positions new in 1967. There are also increases of $97,000 for centrally furnished services from the "National Institutes of Health Management Fund."

PROGRAM DIRECTION

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	57	$605,000	59	$626,000	+2	+$21,000
Other expenses	--------	652,000	--------	689,000	--------	+37,000
Total	57	1,257,000	59	1,315,000	+2	+58,000

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 $32,000 and 2 positions will provide additional planning, programming, budgeting and the cost-effectiveness programs. Analyses will be undertaken concerning operations research and systems communications within selected areas, such as automated laboratory operations in cancer research, and increased computer technological utilization in research areas.

An increase of $9,000 is requested for mandatory items such as annualization of wage-board pay increase in 1967, offset by one less day of pay in 1968 and non-recurring items. There are also increases of $17,000 for centrally furnished services from the "National Institutes of Health Management Fund."

New positions requested, fiscal year 1968

	Grade	Annual salary
Laboratory and clinical research:		
Medical officer (1)	GS-17	$22,760
Medical officer (2)	GS-16	40,150
Scientist (2)	GS-16	40,150
Research assistant (3)	GS-7	19,353
Animal caretaker (5)	WB-3	20,150
Subtotal (13)		142,563
Collaborative research and development:		
Medical officer (3)	GS-16	60,225
Branch chief (1)	GS-15	17,550
Medical officer (2)	GS-15	35,100
Do	GS-14	30,212
Research assistant (2)	GS-6	11,734
Clerical assistant (6)	GS-5	31,986
Clerical assistant (2)	GS-4	9,552
Do	GS-3	8,538
Clerical assistant (3)	GS-2	11,775
Subtotal (23)		216,672
Biometry, epidemiology, and field studies:		
Statistician (1)	GS-11	9,221
Do	GS-9	7,696
Subtotal (2)		16,917
Program direction:		
Public Health Program Specialist (1)	GS-16	20,075
Do	GS-15	17,550
Subtotal (2)		37,625
Total new positions, all activities (40)		413,777

TUESDAY, APRIL 11, 1967.

NATIONAL HEART INSTITUTE

WITNESSES

DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL HEART INSTITUTE
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
R. H. HENSCHEL, EXECUTIVE OFFICER, NATIONAL HEART INSTITUTE
JOHN H. REEDER, BUDGET OFFICER, NATIONAL HEART INSTITUTE
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	5,383	5,768	5,846
11.3	Positions other than permanent	198	229	229
11.5	Other personnel compensation	64	79	79
	Total personnel compensation	5,645	6,076	6,154
12.0	Personnel benefits	630	658	662
21.0	Travel and transportation of persons	240	275	294
22.0	Transportation of things	108	98	98
23.0	Rent, communications, and utilities	168	177	190
24.0	Printing and reproduction	22	35	35
25.1	Other services	1,076	1,424	1,679
	Project contracts	4,243	16,064	17,121
25.3	Payment to "National Institutes of Health management fund"	6,323	6,555	7,430
26.0	Supplies and materials	1,000	1,101	1,590
31.0	Equipment	483	722	958
41.0	Grants, subsidies, and contributions	119,703	130,496	131,763
42.0	Insurance claims and indemnities	2		
	Subtotal	139,643	163,681	167,974
95.0	Quarters and subsistence charges	−19	−20	−20
99.0	Total obligations	139,624	163,661	167,954

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	690	695	704
Full-time equivalent of other positions	43	55	55
Average number of all employees	629	687	696
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	96,163	105,996	106,628
(b) Fellowships	6,095	6,975	7,439
(c) Training	17,445	17,525	17,696
Total, grants	119,703	130,496	131,763
2. Direct operations:			
(a) Laboratory and clinical research	10,468	11,469	13,135
(b) Collaborative research and development	1,381	16,428	17,526
(c) Biometry, epidemiology, and field studies	1,763	1,590	1,727
(d) Training	250	289	295
(e) Review and approval of grants	2,346	2,571	2,663
(f) Program direction	558	818	845
Total, direct operations	16,766	33,165	36,191
Total program costs, funded [1]	136,469	163,661	167,954
Change in selected resources [2]	3,155		
10 Total obligations	139,624	163,661	167,954
Financing:			
16 Comparative transfers to other accounts	1,540	781	
25 Unobligated balance lapsing	295	315	
New obligational authority	141,459	164,757	167,954
New obligational authority:			
Current authorization:			
40 Appropriation	141,462	164,770	167,954
41 Transferred to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−3		
"Operating expenses, Public Buildings Service," General Services Administration (80 Stat. 674)		−13	
43 Appropriation (adjusted)	141,459	164,757	167,954
Relation of obligations to expenditures:			
10 Total obligations	139,624	163,661	167,954
70 Receipts and other offsets (items 11–17)	1,540	781	
71 Obligations affecting expenditures	141,164	164,442	167,954
72 Obligated balance, start of year	65,827	92,773	118,775
74 Obligated balance, end of year	−92,773	−118,775	−139,764
77 Adjustments in expired accounts	−2,850		
90 Expenditures	111,368	138,440	146,965

[1] Includes capital outlay as follows: 1966, $432,000; 1967, $722,000; 1968, $958,000.
[2] Selected resources as of June 30 are as follows: Unpaid, undelivered orders, 1965, $1,299,000 (1966 adjustments—$13,000); 1966, $4,441,000; 1967, $4,441,000; 1968, $4,441,000.

Mr. FLOOD. We have this morning Dr. Donald Fredrickson, Director of the National Heart Institute. Do you have any special colleagues you would like to present, Doctor?

Dr. FREDRICKSON. Yes, Mr. Chairman. Mr. Richard Henschel, the Executive Officer of the Heart Institute on my left, and behind me is Mr. John Reeder, the budget officer.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. We have a biographical sketch of Dr. Fredrickson which we will insert at this point in the record.

(The biographical sketch follows:)

Name: Donald S. Fredrickson, M.D.
Position: Director, National Heart Institute.
Birthplace and date: Canon City, Colorado; 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–present: Director, National Heart Institute; Chief, Laboratory of Molecular Diseases, NHI; 1962–1966: Head, Section on Molecular Diseases, Laboratory of Metabolism, NHI; 1961–1966: Clinical Director, NHI; 1955–1961: Member, Senior Research Staff, Laboratory of Cellular Physiology and Metabolism, NHI; 1953–1955: Clinical Associate, NHI; 1952–1953: Research Fellow in Medicine, Massachusetts General Hospital, Boston, Mass.; 1950–1952: Assistant in Medicine, Peter Bent Brigham Hospital, Boston, Mass.; 1950–1951: James Jackson Cabot Research Fellow in Medicine, Harvard Medical School, Boston; 1949–1950: House Officer, Peter Bent Brigham Hospital, Boston, Mass.

Association memberships: American Heart Association, American Association of 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 Medical Association, Phi Beta Kappa, Phi Kappa Phi.

Special awards, citations, or publications: Honorary Member of the Medical Society of Sweden, Co-Editor, 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 co-author of approximately 100 scientific papers.

General Statement

Mr. Flood. I see you have a statement. I presume you want to read your statement?

Dr. Fredrickson. I would like to, sir.

Mr. Flood. Proceed, Doctor.

Dr. Fredrickson. Mr. Chairman and members of the committee, the mission of the National Heart Institute is to conduct and support research to improve our understanding of the cardiovascular system in order to develop means of prevention, relief, or cure of disorders affecting its functions. The cardiovascular system includes the heart, blood vessels, and the blood itself. The functions of the lungs and kidneys are so interrelated with the circulation that they must inevitably be included in our purview; and the same is true of certain endocrine glands, of the autonomic nervous system, and of many other tissues whose metabolism and secretions affect the rhythm of the heart, the strength of its contractions, the content of the blood, and the caliber and integrity of blood vessels. We must also be concerned with the study of man's environment, his diet, his physical activity, his emotions, his genetic inheritance, and embryonic development where such factors bear on the ability of his circulatory system to perform well its central function of carrying blood to sustain life in all tissues of the body.

Deployed across this broad front, the programs of the National Heart Institute supported more than 2,200 research projects at more than 420 universities, hospitals, and other institutions during 1966. Their achievements were recorded in more than 3,800 papers and abstracts added to the scientific literature during the year. Summaries of some of their results appear in the highlights and special reports to be submitted to the committee. Thus, I shall confine these remarks to a brief discussion of several current programs that I believe will be of particular importance and interest to the committee.

MAGNITUDE OF THE HEART DISEASE PROBLEM

At this point, Mr. Chairman, I believe it would be helpful to the committee if I might bring out some recently available information

that helps put into perspective the relative magnitudes of several diseases with which the Institute is particularly concerned. Of approximately 1.8 million Americans who died in 1965—and these are the latest figures we have—about 1 million deaths were attributed to cardiovascular disease. These diseases accounted for about two out of three deaths among Americans over the age of 65, but they also caused about 250,000 deaths among those under 65. As Dr. Shannon brought out in his earlier testimony, high blood pressure, or hypertension, is probably the most common cardiovascular disease in terms of its incidence, but it is not the greatest killer. In fact, there has been a very gratifying decline in mortality from hypertension in the past decade.

The death rate fell nearly 46 percent during the period 1955 through 1965. Much of this is due to the wide use of better drugs for the control of the more severe forms of hypertension. High blood pressure is also the cause of stroke in many instances; and here, too, we have seen a decline in the death rate from all cerebrovascular disease, which includes strokes, over the same period. In 1965 the total deaths due to stroke were on the order of 201,000 in the United States. Due mainly to improved methods of diagnosis and therapy, we have also seen a decline in the death rates from rheumatic and congenital heart diseases, which accounted for 15,000 and 10,000 deaths respectively, in 1965.

The major cause of cardiovascular deaths is atherosclerotic heart disease. This includes coronary heart disease and heart attacks. Nearly 560,000 deaths were attributed to this disorder in 1965. Here there is not much basis for optimism because the death rate from this disease actually rose about 11 percent during the decade 1955 to 1965. It has been increasing in all age groups over the age of 35. The underlying abnormality, atherosclerosis, which is also the basis of many deaths from strokes, outweighs all other disease problems in mortality. It understandably accounts for the major share of our activities in heart research. This research extends from attempts, on the one hand, to develop a better understanding of the causes of atherosclerosis and thus develop means of preventing it to, on the other hand, a search for means to assist the survival of those who are now suffering from this widespread disease.

ARTIFICIAL HEART MYOCARDIAL INFARCTION PROGRAM

One of the programs important in this regard is the artificial heart program.

To accelerate the development of devices to support or substitute for the failing human heart, the Congress appropriated $3.8 million in fiscal year 1966 and $13.7 million in 1967 to support an organized program of artificial-heart development. The past year has been the first successful use of the DeBakey-type heart pump to assist the heart in the early days of recovery from cardiac surgery. The Kantrowitz device has had initial trial in man, and at least six other different types of pumps to assist or replace the left ventricle have been brought to the stage of animal testing. The Institute has, to date, let 32 contracts and by the end of this fiscal year will probably obligate funds for a total of 50 contracts to further research and development of such devices.

The experience gained so far has allowed us to reach this year a major decision concerning the proper course that this program should

now take. It has become evident that immediate steps must be taken to assure that our knowledge of the effects of mechanical assist devices on the heart and body of the recipient progresses apace with the development of the devices themselves.

It is foreseen that the major need for artifical assist devices will occur in the treatment of acute heart attacks, or myocardial infarction, a national health problem of staggering dimensions. Every year about 750,000 Americans suffer such attacks and, by conservative estimates, more than 350,000 are killed by them. We have no valid estimate of how many might be saved by appropriate mechanical assistance for their failing hearts, but we believe that the number may be substantial, indeed.

This objective and the development of an artifical heart can be logically and efficiently coordinated under a single program. An artificial heart-myocardial infarction program has therefore been established. Its activities fall into two branches.

The bioengineering branch is concerned with the development and refinement of heart-assist devices. Its short-term objectives will be confined to pumping systems designed to provide temporary assistance to sustain a damaged heart until it has mended sufficiently to resume its circulatory obligations. The engineering requirements of this problem, dealing with materials, power sources, and control mechanisms, can be forecast reasonably well. Systems development techniques will be used to the maximum feasible extent.

Experience gained during the development of temporary devices will provide an essential base of knowledge from which it will be possible to drive toward the more ambitious goal of a permanent replacement for hearts damaged beyond salvage. Resources can eventually be committed toward development of a permanent implanted artificial heart in deliberate steps after the closure of present gaps in scientific knowledge concerning the body's ability to accept and use such a device.

Meanwhile, the medical branch of this joint program is developing a program to complement the bioengineering one. Its aim is to increase our understanding of myocardial insufficiency and to improve its clinical management. From six to 12 acute coronary care units in major institutions will receive special support enabling them to provide the most advanced care of heart attack victims while conducting sophisticated and systematic observations on the acute attack and its most dangerous complications. We need to learn more about the presently unpredictable clinical course of myocardial infarction, about causes of death and determinants of survival. And we propose to bring all the talent we can muster to bear on many unsolved problems in diagnosis and therapy. This targeted program will also provide the best circumstances for definition of the role of heart-assist devices in the clinical management of myocardial insufficiency.

The artificial heart-myocardial infarction program thus represents a two-pronged attack. Coordinated under single direction, it will seek to direct the efforts of clinicians, biologists, and engineers against a single disease target on an almost unprecedented scale. For this reason, and because of the signal importance of its goal, we look upon this program as one of the most significant biomedical efforts of our time.

DIET HEART FEASIBILITY STUDY

At the same time that the Institute is mounting the artificial heart-myocardial infarction program, it must increase its efforts to prevent coronary artery disease and myocardial infarction by attacking the underlying cause, the disease atherosclerosis. The evidence is now quite good that the incidence of coronary occlusion in young men will decrease if we can reduce the level of certain plasma fats or lipoproteins in Americans. The question is how and at what age we must begin to do this.

Mr. FLOOD. You mean by diet?

Dr. FREDRICKSON. We are not certain that diet is the only way to do this. This brings me to the next point, Mr. Chairman, that the diet heart feasibility study which was begun in fiscal year 1962 has been completed and its report is now being prepared. It will be available to the Institute for planning purposes this summer. We expect this experiment to provide us with a base for determining whether it is feasible to conduct a large-scale prospective study in which the American diet would be sufficiently altered to ascertain the effect on coronary occlusion.

This feasibility study was designed to answer the question of whether one could alter the diet of a sufficient number of Americans to proceed, if it is deemed desirable, to the next step.

Mr. FLOOD. Especially young Americans.

CORONARY DRUG STUDY

Dr. FREDRICKSON. Yes. Meanwhile, a second major cooperative study, the coronary drug study, is underway. 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. It is progressing smoothly. By December 1967 we expect to have enrolled all 55 participating clinics and the recruitment of the required 8,500 patients to be well underway. The central facilities for coordinating the study, performing the required laboratory determinations, and distributing the necessary drugs are all established and operating.

NATIONAL BLOOD RESOURCE PROGRAM

Another major program of the Institute for which funds were first appropriated in fiscal 1967 is the national blood resource program. Its aim is to provide coordination of research and development in the fields of blood preservation and fractionation and to guarantee allocation of support for efforts to take advantage of newer techniques already applied to the problems of blood fractionation on a laboratory scale. The need for such programing mounts daily. It has become increasingly evident that whole blood transfusions are no longer always desirable or needed, and demand is rising precipitously for separate blood components, such as platelets for treatment of leukemia, antihemophilic globulin for hemophilia, and gamma globulin for protection against infectious diseases.

Mr. FLOOD. I am advised that you lose one-third of the blood storage.

Dr. FREDRICKSON. Yes, that is approximately correct, sir, although

you do not actually lose all of the given pint of blood when it becomes outdated, that is, after 21 days on the shelf, you can still use the whole plasma or the albumin part of the plasma. Other elements, such as platelets and certain proteins are lost however. Thus some of this wastage is unavoidable, at least in the present day.

One must set aside blood for individuals who may need it; but if anticipated demands do not materialize, some of it may then pass its useful shelf life before it can be lifted from reserve. But certainly about 20 to 25 percent of the blood drawn in this country is lost or not used, at least as whole blood. This is one of the problems to which this program is particularly directed. The first aim of this program is to attempt to develop large-scale adaptation of present laboratory methods for fractionating blood.

Mr. FLOOD. Fractionating?

Dr. FREDRICKSON. Fractionating. Today the requirements for blood are changing. They have been changing over the past several years. No longer do physicians want in many instances to give whole blood transfusions. They much prefer to give fractions of blood, either the platelets or specific fractions of the plasma proteins such as antihemophilic globulin, albumin, or gamma globulin to treat infectious diseases. So it is much more useful today to use blood fractions.

Mr. FLOOD. You use this in leukemia.

Dr. FREDRICKSON. Yes. This is one of the reasons for the dramatic improvement in the longevity of patients with acute leukemia.

Such fractionation of blood is wasteful unless it can be reasonably coordinated; that is, if you used one unit of blood solely to obtain its platelets then, without some adaptation or coordination of activities, you might well lose all the rest of the fractions. It is precisely this sort of uncoordinated loss of other elements of blood in order to get one element that we would like to move toward solving, and that is one of the major purposes behind this program.

A program director has been appointed who will work with an advisory group representing the American Red Cross and other agencies most concerned with proper usage of the Nation's blood resource. A program has been developed with a major immediate goal of devising more efficient, highly automated methods for the mass production of medically important cellular and protein fractions of blood.

A second objective is studies of the use of adenine. Adenine is a chemical on which studies have been made by the U.S. Army and others. Its use as a preservative may make it possible to double the shelf life of a single unit of blood from 21 days to more than 40. This process is in use in Sweden today, and we hope to coordinate and fund more studies to determine as soon as we can whether this is entirely safe and desirable.

Other major goals are the development of improved preservation and storage techniques for blood and blood products. Such techniques would go far toward minimizing losses that now result from the rapid deterioration of whole blood and certain fractions under current storage conditions.

In the laboratory, one can freeze blood and blood plasma and greatly increase the storage time. Such techniques, applied on a very large scale, would go far toward minimizing present losses.

Mr. LAIRD. There has been quite a bit of work done with frozen blood.

Dr. FREDRICKSON. Yes, there has. There needs to be more to determine how long it can be stored and what may be the effects of these frozen fractions. We still do not know enough.

Mr. FLOOD. Frozen fractions or frozen blood.

Dr. FREDRICKSON. Both, sir. We still do not know enough to suggest that this be adopted as a wide-scale procedure throughout the country. Some of the other plans for attacking these problems are described in some detail in a special report prepared for the committee. Thus far I have emphasized some Institute programs concerned with coordinated attack upon quite specific disease targets. I should like to turn now to our approach to several other problems identified as requiring well-planned support for optimal use of scientific manpower. These concern the critical need for increasing convergence of the basic science and clinical disciplines upon cardiovascular disorders.

CARIOVASCULAR RESEARCH CENTERS

The Congress supplemented the 1966 and 1967 budgets of the Institute with funds for grants to plan the development of Cardiovascular Research Centers about the Nation. A Cardiovascular Research Center is defined as an organized core group of scientists capable of creative and independent cardiovascular research set up within a university or other institution already engaged in postgraduate training of scientists in many disciplines. Integrated under an outstanding director, the research program should include work of individuals representing excellence not only in medicine but in other biological and physical sciences. It should also bring a broad range of scientific techniques to bear on clinical problems. The staff and facilities of these Centers will attract and train a substantial number of high-level graduates and thus help to meet increasing needs for cardiovascular research personnel.

The Institute foresees the development of 10 to 12 such Centers within the next 5 to 6 years. The Center grant should provide funds for renovation of physical facilities where necessary; for the care of research patients; for essential supporting personnel; and for equipment, supplies, and other research program needs. The annual cost per Center, once it is fully operating, will be in the neighborhood of $4 million.

CLINICAL TRAINING GRANT PROGRAM

As a necessary complement to its programs for training carovascular research scientists, the Heart Institute launched a new clinical training grant program last year. The program is designed to help meet serious manpower shortages developing in such critical areas as cardiovascular anesthesiology, diagnostic radiology, hematology, pharmacology, and other related disciplines. This program does not support routine training to fulfill ordinary requirements for a professional degree. It is intended to train physicians to special competence in the most advanced diagnostic and therapeutic techniques developed through research in their particular fields.

The goal of the program is to provide such training to at least 2,800 physicians during the next 5 years. To date, 18 grants have been

awarded to 17 institutions and nine others approved. The continued orderly expansion of this program is necessary to meet the increasing demand for such highly skilled clinicians who can translate the fruits of research to clinical care.

Finally, I should like to call your attention to changes occurring within the NHI intramural research program during the year. The Laboratory of Cardiovascular Physiology was phased out with retirement of its Chief. Two former laboratory sections were elevated to full Laboratory status.

LABORATORY OF BIOCHEMICAL GENETICS

The newly formed Laboratory of Biochemical Genetics, headed by Dr. Marshall Nirenberg, is one of the outstanding laboratories in the world engaged in the exciting and exceedingly important studies of the nature of the genetic code.

In fact, this code was "cracked" in this particular laboratory, at least the first major work was done here.

Mr. FLOOD. What code?

Dr. FREDRICKSON. The genetic code, meaning the code built into the genes of the cell. What was really done by this group was to determine how this code is transmitted from the gene to the other machinery in the cell for putting proteins together. In other words, we have 20 amino acids which are strung together in chains; and the way these are strung together accounts for the differences among the thousands of proteins we have in the body.

The genes tell the cell how to make these proteins. It is the means for transmitting this information which now has been reasonably well worked out. It is of tremendous fundamental importance to all of cellular biology. This is concerned with the instructions passed from generation to generation through deoxyribonucleic acids in the cell nucleus and their translation by ribonucleic acids into the enzymes and structural proteins that determine the nature of all living matter. Using techniques pioneered in this Laboratory, the Institute scientists have worked out nearly all of the 64 possible RNA coding units, or codons, that direct the sequence in which the 20 amino acids are incorporated into protein chains. It has been established that a given amino acid is usually represented by more than one coding unit, and it is now necessary to determine which of these coding "synonyms" is the most important one for each. Also being determined are the parts of the code that serve as "punctuation marks," in genetic messages.

LABORATORY OF MOLECULAR DISEASES

The new Laboratory of Molecular Diseases is concerned, at an entirely different level, with errors in the genetic code resulting from mutations and finding clinical expression in those heritable disorders associated with lipid or lipoprotein metabolism. The frequency of these disorders in the American or other populations has never been determined, although several of them are fairly common and are frequently associated with accelerated development of atherosclerosis. Last year this Laboratory introduced a new system for identifying and classifying such hereditary disorders on the basis of plasma lipoprotein patterns. It is using this system at Bethesda in probably

the largest study in the world on the hereditary lipoprotein abnormalities. The new system provides improved recognition of these defects and also better means for evaluating the effectiveness of diet or drug therapy to correct them.

In conclusion, Mr. Chairman, the request for the National Heart Institute is $167,954,000 for 1968 as compared with an operating level of $163,661,000 in 1967, an increase of $4,293,000. Of the requested increase, $1,267,000 will be allocated for extramural research and training activities as follows: $632,000 for research grants, $464,000 for fellowships, and $171,000 for training grants. The remaining $3,026,000 will be allocated for direct operations, principally for laboratory and clinical research, collaborative studies, review and approval of grants, and program direction.

I shall now be happy to answer any questions the committee might have.

Mr. FLOOD. This is your first appearance?

Dr. FREDRICKSON. Yes, sir, it is.

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

Dr. FREDERICKSON. I have been the Director since mid-November, sir.

Dr. SHANNON. He has been a member of the staff since 1953.

Mr. FLOOD. Then you are not unacquainted with the interest of this subcommittee in this subject?

Dr. FREDRICKSON. I think that is correct, sir.

SUMMARY OF BUDGET REQUEST

Mr. FLOOD. You have an appropriation, as you said, of $163,976,000. Your request for 1968 is $167,954,000. That is an increase of $3,978,000. The increase is less than 2½ percent.

Dr. FREDRICKSON. That is correct.

Mr. FLOOD. I am an old percentage player. You are going backwards. You are backing up; are you not? This won't come close to the way this committee thought you would do business. This won't cover your increased costs of continuing at the current program level.

Dr. FREDRICKSON. It will certainly be a more stringent budget than the Institute has ever had, sir.

Mr. FLOOD. What do you think, Doctor Shannon? Is this progress?

Mr. SHANNON. Mr. Chairman, I can only say that the budget before you does not reflect what we would feel is the scientific opportunity of the Institute, but rather the stringency of the funds available.

Mr. FLOOD. Yes, I know.

Dr. SHANNON. I think it can only be viewed in that light. Within the funds made available to us by the Bureau of the Budget, we have done the best we can in sorting out those things we feel are of immediate urgency, that can be programed for purposeful employment of our resources, and those things that constitute extraordinary opportunities, but which are less amenable to immediate and short-term programs.

Mr. FLOOD. Including the sensibilities of this subcommittee—was that discussed?

Dr. SHANNON. Sir, the Bureau of the Budget did not discuss the sensibilities of the committee.

BUDGETARY RESERVE FOR SAVINGS

Mr. FLOOD. What adjustments did you make to get this saving or this reserve of $315,000 in 1967?

Dr. FREDRICKSON. That reserve was met primarily by reduction in expenses for supplies, equipment and material, and travel.

Dr. SHANNON. These are deferred expenditures, part of the general cost reduction required by the Department. This item you will find in each of the budgets. Again it has been taken where we feel it would hurt least. It does not reflect a change on the part of the Institutes in respect to plans for program development.

NATIONAL BLOOD PROGRAM

Mr. FLOOD. We approved funds over last year's budget to start a national blood program. We talked about this a few minutes ago but tell us just what is your plan for this program.

Dr. FREDRICKSON. We have a definite plan for the blood program. We have a director and he is moving. We are in the process of negotiating a large contract to develop methods for large scale and hopefully automated fractionation of blood as our first step. This is terribly important. Pilot plant operations have been done; they need to be scaled upward. To give you one example, for treating hemophilia there are several ways of getting antihemophilic globulin.

Mr. FLOOD. The public is totally unaware of this business of fractionation of blood. They never heard of this.

Dr. FREDRICKSON. One of the problems is infectious hepatitis carried in blood. The problem of transmitting hepatitis in blood transfusions is tremendously reduced by blood fractionation.

Mr. FLOOD. They know something about that.

Dr. FREDRICKSON. Perhaps, but they do not realize the specific fractions that are now needed for many particular purposes. I think antihemophilic globulin is an excellent example. There are a number of methods of obtaining this material but they are all on a scale inadequate to meet the current needs. Yet it is certain, I think, if we use good pilot plant approaches and developmental research, we should be able to greatly increase our ability to make this fraction and meet the demand. The same is true of gamma globulin, platelets, and the other elements. This will be our major thrust. We hope to make this our major obligation this year.

Secondly, in this same fiscal year we hope to obligate funds for studies of the use of adenine, as I mentioned earlier in my opening statement. This is a very promising way of extending, certainly doubling, the shelf-life of blood once it is drawn from the donor. These will be the steps this year. The budget for 1968 includes an amount of $1,093,000 as the second stage of support for further research and development of the national blood resource program.

Mr. FLOOD. What are you going to do in the next 10 years? What is the future of the blood program?

Dr. FREDRICKSON. I think the future can be determined very much by some studies that we hope to fund particularly next year. These involve several important aspects; one, we would like to examine what is the real need in the United States for blood and special blood fractions. Nobody knows in sufficient detail to anticipate the needs in

the next 10 years. Secondly, we would like to fund studies to determine whether we can computerize or otherwise systematize data in the United States relative to donor or blood availability.

Mr. FLOOD. He has been around a while, has he not?

Mr. LAIRD. I hope he stays.

Mr. FLOOD. I agree.

Dr. FREDRICKSON. The matter of inventory is very important.

Mr. FLOOD. How old are you?

Dr. FREDRICKSON. Forty-two, sir.

Mr. FLOOD. Stick around, we need you.

Dr. FREDRICKSON. The matter of inventory is very important because it may be that we could maintain one on a regional basis or even a national basis—I am not sure how it would be done and therefore we need funds to make an appropriate study—and better anticipate needs and meet them when they suddenly arise. In other words, the current status of information about the needs and the way to meet those needs with regard to the national blood resources is really very inadequate.

Mr. FLOOD. What about a national disaster situation; were you in on that?

Dr. FREDRICKSON. We most certainly want to bring into our advisory group people from agencies representing the national disaster facilities, the Red Cross, the Office of Emergency Planning, the Department of Defense and so forth. At the moment we in the Heart Institute are not participating in an emergency plan for blood.

HISTORICAL SETTING OF NATIONAL BLOOD PROGRAM

Dr. SHANNON. Mr. Chairman, could I comment very briefly on the status of the national blood program in terms of its historical development. I think it is important for the committee to appreciate that there was a very vigorous program on blood in World War II, primarily to satisfy the need of our Armed Forces. This was met so successfully, in terms of the logistics of the operation, that it was believed possible to apply some of the concepts developed during World War II to the civil blood program.

Mr. FLOOD. Except that we lost 25 percent.

Dr. SHANNON. Yes, sir. This I want to come to. The Red Cross, after the war, was the primary distributor of blood.

Mr. FLOOD. The public does not know that.

Dr. SHANNON. No, sir. I realize that. The National Research Council was given charge of developing a national program—to consider problems of blood and blood substitutes and problems of preservation and fractionation—even at that time.

This activity did not prosper primarily because of lack of dollar support from the interested agencies. I might say that NIH, in the late 1940's, was concerned primarily with supporting work that led to increased capability of storing of some of the formed elements but did not have responsibility for the whole program, or really too much to say about the direction the program should take.

It was determined in the early 1950's that the so-called national program was coming to a grinding halt rather rapidly due to lack of technical leadership from any source and due to lack of a coordinating mechanism. At that time it was decided to set up a national program,

centered in the Office of the Surgeon General of the Air Force, and to develop a central staff to coordinate the activities. This was not a wholly successful operation. Although the various agencies did, indeed, contribute to research and development, it was not a very purposeful program, due largely to the different aims and objectives of the different agencies. We became deeply concerned with problems of blood and blood fractions incidental to many of our programs—such as open heart surgery, and the like—for which, we determined, that not only whole blood was essential but that particularly in the future, the need would be more in the realm of fragments of whole blood rather than whole blood as such.

We started fairly extensive developmental work, particularly with Oak Ridge, in physical means of separating whole blood, we found, to our surprise, that—as the service demand on the Red Cross increased during the last 2 or 3 years and as the Armed Forces became more involved with the use of blood rather than with the development process—both the Red Cross and the Department of Defense were withdrawing support for research and development activities in this field. This we learned from fairly extensive discussions with both of those agencies.

It was this withdrawal of support, together with the very broad opportunities that were open, that led to discussions with Mr. Fogarty last year and to the organization of the program at the NIH. The allocation to the NIH was in order to put the program in an operational agency with competence both to define the problem and bring technical capability to bear on the solution.

It was his intent, and I trust that this committee would follow through, to support the activity with a single focus, in proportion to the need, rather than to support the activity through multiple agencies and depend upon this loose aggregation of skills for the eventual solution of such serious problems as this. We, at the NIH, feel that our interests are sufficiently diversified, we feel that we have the management capability, and we feel that we can define the need, both for today and for tomorrow, in a better fashion than is possible by any loose aggregation of agencies. We are quite prepared to stand or fall on our capability to do a good job in this area.

Mr. FLOOD. That was a good statement Dr. Shannon. It may be almost anticlimactic, but I think this special report on the subject should be a part of the record.

(The report follows:)

SPECIAL REPORT: NATIONAL HEART INSTITUTE

THE NATIONAL BLOOD RESOURCE PROGRAM

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 as red blood cells, platelets, albumin, or clotting factor concentrates 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 remain indispensable in those clinical situations where shed blood must be replaced or circulating blood volume expanded. But as medical science grows steadily more discriminating in the employment of blood and blood products, the demand for specific blood fractions

will rise much more rapidly than that for whole blood and plasma. Fortunately, the need for these fractions need not outstrip the supply, for developments in engineering and technology have probably made feasible the mass production of blood components and the automation of many of the steps involved in blood processing.

But foreseeable needs can be met only if the national blood supply is carefully husbanded. This will require a national plan for the modernization of blood production and distribution systems, the mobilization of resources and coordination of effort. No longer can we afford to rely on haphazard approaches to the solution of problems as they become critical: the claims on the National blood supply are too great, too varied, and too conflicting. In the face of an annual blood supply of 6.5 million units, only the most carefully planned use of this resource can meet the large need for whole blood and plasma plus needs for platelets from 2 million units, antihemophilic globulin from 1 million units, gamma globulin from 4.5 million units, and a steadily growing need for red blood cells and other fractions.

Because it has become apparent that the persistent use of blood is exceedingly wasteful, one of the major goals of the National Blood Resource Program is to effect economies in the use of donor blood. We feel that the potential savings that might accrue from more efficient management of blood resources would repay many times over the investments necessary to achieve these savings.

It is difficult to place a dollar value on a unit of blood; but, even if one considers only the tangible costs of processing it, $10 per unit is probably a conservative estimate. In 1965, approximately 1,800,000 units of blood were drawn that were never transfused. This blood became outdated in storage, the red cells and other cellular components were discarded, and only a part of the plasma was saved for fractionation. Thus, the loss for 1965 alone was approximately $18,000,000.

More important than the dollar loss was the fact that blood components were not available to every patient who needed them. Life-saving components, such as antihemophilic globulin and blood platelets, were available in amounts representing only a small fraction of the national requirement. With these and other demands for blood components unsatisfied and steadily increasing, such wastage of blood is becoming intolerable.

The projects to be described in this report represent some of the approaches aimed at the solution of identifiable problems. Each of these approaches should be placed on a firm foundation through a systematic study of its feasibility, its relationship to other program goals, and its probable effectiveness in reducing waste and in increasing the yield and availability of blood products from existing blood resources. This in-depth study should not be a one-shot project. It should provide a basis for the continuing evaluation of blood supplies and their utilization, of changing needs and developing opportunities, and of the possibility and probable cost effectiveness of new projects proposed in the course of the program.

The intelligent direction and orderly development of the National Blood Resource Program will require finding answers to questions such as these: What are the factors contributing to the wastage of donor blood and what is the relative importance of each? To what extent might the institution of a new technique or new instrument effect savings in blood and money? Will these savings justify the probable cost of developing the proposed technique or instrument? Will success in extending the shelf life of blood stored under standard conditions eliminate or reduce the need for developing instrumentation and techniques for freezing blood in large quantities? If not, what should be our capabilities for freezing and storing frozen blood now and in future years? Can military needs for blood and blood products and the potential military drain upon civilian sources be foreseen and planned for? To what extent might a national or regional daily shelf inventory of blood and blood products decrease current inequities between supply and demand? How many "bleeders" are there in the United States and what are their annual needs for antihemophilic globulin and other blood-clotting factors? Can the anticipated need for platelet concentrates be met by supplying fresh platelets, or must we invest in the development of methods of platelet preservation?

These are examples of a very large number of questions that need to be answered now or at intervals in the future. Out of each answer may arise still other questions. But a research and development program, guided by a continuing study of current progress, present needs, and future goals, offers the best and

most economical means of providing an adequate blood and blood component supply for the clinical needs of our population and the research needs of our scientists.

Hopefully, as blood fractions become more widely available and physicians become fully attuned to their clinical application, the use of whole-blood transfusion will decline. The use of a specific blood fraction to serve a specific clinical purpose would increase the effectiveness of blood therapy and eliminate many transfusion complications while simultaneously making the rest of the contents of a bottle of blood available to serve other urgent medical needs.

RESOURCES

Fortunately, we already possess the scientific manpower and technological resources needed to develop and implement a coordinated program of blood collection, processing, and utilization. These resources need only to be mobilized, strategically deployed, and their efforts integrated into a unified attack on the problems that confront us.

A number of Institutes at NIH conduct and support programs of research relevant to these problems. NHI, for example, invests heavily in research on blood banking and preservation; immunological considerations in blood therapy; blood coagulation and clot dissolution; and the causes, diagnosis, and clinical management of hemorrhagic diseases. The National Cancer Institute supports research on blood-forming tissues and blood components, particularly such formed elements as platelets and white blood cells. The National Institute of Arthritis and Metabolic Disease has a special research interest in all types of anemias and the National Institute of Allergy and Infectious Diseases in immunological proteins of plasma. The Division of Biologics Standards has the Federal responsibility for quality control of blood and blood products shipped in interstate commerce.

The most important resource is, of course, the American Red Cross, whose nationwide chain of 56 blood centers collected, processed, and distributed nearly 3,000,000 units of blood during 1965. The Red Cross also spends about $1,000,000 annually for blood research and many NIH-supported research projects are carried out in Red Cross Laboratories. Their nationwide network of facilities and their special expertise in the handling of blood and blood products will be indispensible assets.

Thus, while it will be headquartered in the National Heart Institute, the National Blood Resource Program will be a cooperative venture requiring close teamwork and liaison between NHI, a number of other Institutes of NIH, and other Federal and non-Federal agencies.

The Chief of the NHI office for the National Blood Resource Program also bears responsibility for coordination of the Institute's grant-supported activities in the fields of hemorrhagic diseases and thrombosis and thrombolysis. The close interrelationships of all these activties provides this office with a knowledge of the nationwide programs in hematology that will enhance the effectiveness of its direction of the Blood Resource Program.

THE PROGRAM

The National Blood Resource Program will direct research and development activities concerned with improving methods of preservation for blood and blood components and with modernizing and automating blood processing and fractionation. The goal is a modern, large-scale system capable of supplying comprehensive blood component services on a national scale with minimal waste and maximum economy. In the discussion that follows, each of the various blood fractions will be taken up separately with regard to their present and potential value to research and clinical medicine and current approaches to the solution of problems involved in their large-scale production.

Red Blood Cells can restore the oxygen-carrying capacity of the blood in patients acutely anemic because of blood loss or chronically anemic because of some disease state interfering with normal red-cell production. Of all blood components, red cells are needed in greatest quantity; yet there is an enormous annual waste of them.

The chief reason is that when the whole blood or red-cell suspensions are stored at 4° C, as is the practice in most hospitals, the red cells begin to deteriorate after 3 weeks, become unsafe for medical use, and must be discarded. In view of unavoidable and unpredictable fluctuations in local blood supplies and in the clinical demands upon them, some wastage of red cells may be inescapable; but losses could be minimized if the shelf life of red cells could be extended.

One promising approach is the use of additives to prolong red-cell survival under standard storage conditions. Studies by the U.S. Army indicate that one of the most promising of these additives is adenine, a preservative that appears to double the shelf life of whole blood stored at 4° C.

Adenine is a precursor substance in the generation of adenosine triphosphate (ATP), a high-energy compound that powers the energy-consuming processes of cell metabolism. It may be that addition of this substance to blood improves red-cell survival by enabling these cells to generate enough ATP to sustain essential metabolic processes during storage at low temperatures.

Intensified testing of adenine and other blood preservatives is a high-priority goal of the program, for even limited success could result in substantial savings of whole blood and red cells.

It is also possible to preserve red cells for prolonged periods by freezing and storage at very low temperatures, but the process is presently cumbersome and expensive. Red cells are destroyed by freezing unless they are first exposed to gradually increasing concentrations of glycerol solution. Then, prior to use, the cells must be thawed and the glycerol removed in another time-consuming operation.

Some unanswered questions remain concerning the final glycerol concentration to be achieved before freezing, the rate of freezing, and the temperature of storage to produce best results; but it should prove possible to preserve blood cells almost indefinitely when this technique is perfected. It also appears likely that the whole process can be automated. The major problems are 1) the development of plastic containers that retain strength and pliability during prolonged storage at temperatures as low as −120°C; and 2) the design of large, low-temperature storage rooms providing automatic storage, retrieval, and inventory control. (The required temperatures would not permit personnel to enter the storage facility.) These problems are not unsurmountable.

Another means of minimizing whole blood or red-cell losses would be a national or regional daily shelf inventory. Through the use of computers and air transport, it should be feasible to meet or forestall blood shortage developing at any given hospital of a region by drawing on blood surpluses of other hospitals in that region.

A regional inventory of rare blood donors could also eliminate many problems. A Boston surgeon's need for 12 units of a rare blood type for open-heart surgery might be met, for example, by summoning donors known to reside in the New York area to a local blood center, then shipping the blood to Boston. In many instances, shelf outdating of rare blood could be prevented entirely by drawing on donors only when the need is apparent.

Program plans call for studies to determine the feasibility of such inventory systems.

An important source of waste of blood resources is the use of whole blood in situations where red cells or other cellular components of blood are called for, but are not available. Much of this waste could be avoided if automated equipment for separating the cellular components from blood were available in large, strategically located blood centers. Such equipment is being developed by IBM under contracts with the National Cancer Institute. The system is desiged for rapid, continuous flow operation and yields almost pure fractions of red cells, white cells, platelets, or plasma. Some further engineering refinements are needed, as are studies of the viability of cellular fractions produced by the system. However, when perfected and installed in key blood centers, the system will be a major step toward meeting the steadily growing need for blood components.

White Cells (leukocytes) are vital to the body's defense against infection. In cancer, leukemia, and certain allergic states, circulating leukocytes are frequently diminished in quantity or impaired in functional quality. As a result, the patient is susceptible to serious infections that may not respond to antibiotic treatment. Preliminary evidence suggests that transfused white cells can be beneficial in such cases.

Leukocyte transfusion may also have value in organ transplantation. If the transplant is to "take," the immunological defenses of the recipient must be suppressed by drugs or x-ray. The threat of infection may be reduced by transfusing the recipient with leukocytes from the organ donor. These leukocytes not only confer temporary protection against infection, but are also compatible with the implanted organ.

The white cells are readily fractionated by the cell separation instruments previously described. It is probable that the instruments can be adapted to separate the several different types of leukocytes.

Platelets, the smallest cellular components of blood, play a prominent role in the initiation of coagulation, in the formation of clots, and in the maintenance of the blood-vessel integrity.

Leukemia patients often have low circulating platelet levels, either as a result of the disease itself or as a toxic reaction to the drugs used in treating it. Drug treatment of solid tumors also frequently reduces platelet levels. Such platelet deficiences can result in serious, often fatal hemorrhage.

Although it has been demonstrated that transfusions of fresh platelets can be life-saving in such patients, adequate platelet therapy is available in only a few medical centers. A single day's treatment may require platelets from the blood of as many as eight donors, and it may be necessary to repeat the treatment several times to see the patient through a single hemorrhagic crisis. A conservative estimate of the national need would be about two million platelet units a year. (One unit equals the platelets from one pint of blood.)

In order to meet this need, a number of difficulties must be overcome. Platelets are extremely fragile and have a marked tendency to adhere to foreign surfaces and to each other, which makes them difficult to handle. Because they cannot withstand storage at 4° C, platelets must be separated from freshly drawn blood and used within 6–12 hours. Furthermore, present methods of processing platelets are so costly and time consuming that few blood banks are able to supply their local needs.

Two recent engineering developments promise a solution. The first is the automated cell fractionator, described earlier, which rapidly removes platelets from individual bottles of blood. The second is a modification of the same instrument that enables it to receive blood directly from a donor's vein, remove the platelets, then return the rest of the blood to the donor. Using this modification, many more platelets can be safely obtained from a donor at a single bleeding. Models of these instruments are already in operation and two or three years of further developmental work can perfect them.

Another approach to the platelet supply problem is low temperature storage. Although platelet freezing is not yet practical, recent experiments suggest that effective techniques may eventually be developed. Present freezing techniques tend to impair the platelets' biological function and produce unacceptably low yields (only 20–30% of the theoretically possible yield), but the quest continues for more efficient methods. These are urgently needed for conservation and efficient utilization of the national supply.

Plasma, the fluid or non-cellular part of blood, is used as a source for a variety of proteins and as a therapeutic agent in cases where rapid blood-volume expansion is necessary, as in shock, burns and severe hemorrhage. Plasma from outdated whole blood is a suitable source of proteins. In blood bank practice, as stored blood reaches the end of its shelf-life, the cells are separated and discarded and the plasma pooled in large containers for protein fractionation. However, plasma for therapeutic use must be derived from fresh blood. It may be frozen in individual units and kept indefinitely.

The most nagging problem relative to the use of plasma, as with whole blood, is the danger of transmitting hepatitis virus. A small but significant proportion of apparently healthy donors carry the virus in their blood stream, but there is presently no way of demonstrating its presence or absence in a unit of blood, plasma, or protein fraction. Infusion of plasma from individual donors carries some risk of hepatitis transmission, but the risk is greatly compounded by pooling the plasma from many donors; hence pooled plasma is preferably not used in treating patients. A method for reducing the risk of hepatitis transmission in blood and blood components is urgently needed.

Plasma production from blood can be greatly facilitated by the IBM cell separator, previously described, which not only provides specific blood fractions, but also increases the plasma yield from a bottle of blood by 25 percent.

Plasma contains a wide variety of proteins that differ in chemical composition and in physiological function. Chemical fractionation methods take advantage of the fact that the different proteins precipitate from ice-cold plasma at different rates as increasing concentrations of salts of alcohol are added. However, in large-scale production, the yield by this method is very low, sometimes only 20–30% of actual protein content.

No significant improvements have been made in these procedures since 1950, and reexamination of the technology is long overdue. New methods of protein

fractionation, developed for use at the laboratory level, may prove adaptable to the processing of large batches of plasma; and recently developed chromatographic and electrophoretic techniques should be studied for possible application to the production of special protein fractions.

The program also proposes to explore the possibilities of an automatically controlled system for the separation of the major plasma proteins: antihemophilic globulin, gamma globulin, albumin, and fibrinogen. Feasibility studies will have to be carried out to determine whether a continuous flow system, built on the same principle as the cell separator, will be applicable to protein fractionation. If basic experiments in the first year give promising results, perfecting instruments may require two additional years. If not, attention should then be turned to automation of the traditional fractionation procedures. The objective in either case is to improve purity, uniformity, and yield of the fractions and to increase the efficiency and speed of the production system.

Of the many plasma proteins, five fractions are of special clinical importance and are discussed in the following section.

Albumin, one of the most abundant proteins in blood plasma, is used clinically for the restoration of blood volume, in hemorrhage, burns, or shock. It is an effective substitute for plasma and, since the processing of albumin frees it of hepatitis virus, would find much wider medical application if it were more readily available. The American Red Cross produced 60,000 units of albumin in 1965, about half of the national supply.

Gamma Globulins are a family of protein molecules that includes all known antibodies to infections diseases. One of the most important uses of gamma globulin and its subfractions is the protection of individuals who are in danger of infection either by reason of exposure or lowered natural resistance. Antibody fractions for use in protecting against or treating a specific illness are obtained from donors whose gamma globulin fractions are known to be rich in antibody against that disease by virtue of relatively recent infection or immunization.

There is no way of accurately predicting the national demand for gamma globulin during the next five years. One estimate of the requirement for military use alone is that amount which could have been derived from the entire six million units of blood drawn in the U.S. in 1965. There is a rapidly increasing demand for gamma globulin for civilian medicine as well. It is important in preventing or controlling infections in patients with hereditary gamma-globulin deficiencies and is finding increasing use in pediatric practice for the control of chronic infections in infants who have low levels of circulating antibodies. In 1965 over seven million cubic milliliters of gamma globulin, derived from about 1.5 million units of blood, were distributed for use in a wide variety of clinical conditions. A conservative estimate of annual need is about three times this amount.

Fibrinogen, the third most abundant protein of plasma, is the precursor of fibrin, the structural substance of blood clots. Thus it is a vital element in the body's defense against hemorrhage. In clinical medicine, it is used to treat hemorrhage complicating surgery and childbirth and to control hemorrhagic crises in patients who are congenitally deficient in this clotting factor. Although present-day production methods are adequate to meet the national needs for fibrinogen, the purity of present preparations leaves much to be desired. Improvement in purity could be effected by modernization of protein fractionation techniques.

Antihemophilic Globulin (AHG) is one of a series of proteins that participate in the clotting of blood. The congenital absence of this clotting factor results in the bleeding disease known as hemophilia A, or classical hemophilia. Victims of this disease are subject to life-threatening hemorrhage from even minor injuries. A tooth extraction may result in hemorrhage so severe as to require 30 to 50 transfusions to preserve life. Spontaneous, often crippling bleeding into the joints and other internal hemorrhages are constant threats. It has been estimated that there are about 100,000 "bleeders" in the United States, perhaps half of them with classical hemophilia; but the tax that hemophilia imposes on the national blood supply is much larger than the incidence of the disease would suggest.

The coagulation defect of hemophilic patients can be corrected (temporarily) only by supplying the missing clotting factor through transfusions of whole blood, plasma, or concentrates of antihemophilic globulin. The clinical use of AHG concentrates avoids many problems encountered with transfusions of whole blood or plasma for the prevention or treatment of hemorrhagic crises of hemophilia. The calculated annual need for AHG is that amount which would be

derived from one million units of blood. Red Cross scientists have developed pilot scale methods to produce a highly effective concentrate from blood plasma. An important public health objective is to provide every known hemophiliac with an appropriate dose of AHG to keep in his possession for emergency use.

There is a special problem relative to the production of AHG which complicates the entire process of blood fractionation. It is such an unstable protein that only freshly drawn blood can be used as a source. Further, AHG must be the first protein component removed from the blood, for the processing for other components will destroy it. Unfortunately, the processing required for removal of AHG is destructive to platelets, whereas the prior removal of platelets by present techniques is damaging to AHG. A system of blood fractionation must be devised which will protect both of these factors. Research on different platelet-production methods may provide a solution to this dilemma.

Specific Immune Globulins are presently finding only limited application in medicine, but their clinical importance will doubtlessly increase. Hence provision should be made for their development and production in quantities sufficient to meet anticipated research and medical needs.

Immediately after an infection or recent vaccination, an individual's levels of antibody against the offending organism rise to very high levels. They so dominate his gamma globulin fraction that, for practical purposes, it becomes a specific immune globulin.

Such high-titer specific globulins are becoming increasingly important in therapeutic use. For example, vaccinia immune globulin (VIG) is the only effective treatment for the serious infection which sometimes follows smallpox vaccination. VIG is found in highest concentration in the blood of individuals who have been vaccinated 4–6 weeks previously. The American Red Cross produced and distributed 1700 doses of VIG in 1965.

Tetanus and measles immune globulins, now being marketed, and rabies immune globulin, now under study, may provide promising new approaches to the prevention and treatment of these diseases. Perhaps more important than any of these is malaria immune globulin, now in the early development stage, which may prove useful in the control of strains of malaria resistant to currently available anti-malarial drugs.

CONCLUSION

The goals that the Blood Program has set for itself thus far are realistic, and it is probable that they can be achieved within a reasonably short time. Many problems involved in the large-scale production of blood fractions are fairly sharply defined and their solution appears to lie within the capabilities of present technology; thus it is possible to attack these problems through negotiated grants and contracts for research and development with precisely specified aims. However, these highly targeted projects supplement, rather than replace or compete with, NIH grant-supported research in the field of hematology. In most instances, it has been the broad base of knowledge gained through grant-supported research that has made such targeted research projects possible. Similarly, the steady broadening of this research base through the orderly expansion of grant-support programs in hematology will be essential to the definition and achievement of new program goals. The research-grants program can be likened to the coarse-focus wheel on a microscope, the negotiated grants and contracts program to the fine-focus wheel. The proper employment of both is essential to produce optimum results in the shortest time.

COOPERATIVE DRUG STUDY

Mr. FLOOD. We added funds for the cooperative drug study so that you could proceed according to a plan which has been set out. How is that program progressing? Does this 1968 budget provide funds to continue according to the plan?

Dr. FREDRICKSON. Yes, it does. It is enough to maintain the program at the expected level of operation in 1968. I think this program will reach its full operating level, which will bring it to a maximum of about $4.6 million in 1969. There is a gradual recruitment of individuals.

Mr. FLOOD. Yes, we were told that.

Dr. FREDRICKSON. We are about on schedule. We are on schedule in terms of the number of clinics. We are slightly behind, but not seriously so, in the recruitment of patients. We are aggressively pushing this program. I think it is going to work. It is a tough one to mount, and is one of the largest cooperative studies ever conceived. But, we intend to make sure it works despite the difficulties.

Mr. FLOOD. We were not told about that. This is difficult?

Dr. FREDRICKSON. This is very difficult.

Dr. SHANNON. Mr. Flood, I held back on agreeing to the study for a full year because I was not convinced that the preparatory work had been completed to an extent that would insure the success of the program.

Mr. FLOOD. Where does the difficulty lie?

Dr. FREDRICKSON. The difficulty in any study of this sort, involving the commitment of a large number of patients over a long period of time, lies in the willingness and the ability of the subjects themselves to stay with the study. You have to allow for a 30 percent dropout rate when you plan such a study. This is costly. But human factors being what they are, you cannot plan to do such a study without this much expectation of slippage. So it is in the recruitment and maintenance of the people in the study where the difficulties lie.

Dr. SHANNON. I would say this in part, determined by the espirit de corps of the individual clinics that conduct the study. The Director of the Heart Institute can only hope that he has selected good groups who will sustain an effort that will last no less than 7 to 8 years for the end result. In the face of changing personnel in the individual clinic, there must be an institutional commitment.

Mr. FLOOD. Will this heart, cancer and stroke program, if it gets off the ground, help or hurt? It cannot hurt.

Dr. SHANNON. No, sir. It will provide the way for applying the knowledge that is derived from studies such as this. But it will not determine the effectiveness of the study itself.

Mr. FLOOD. You also have a special report on the subject. We will place it in the record at this point.

(The report follows:)

ATHEROSCLEROSIS AND CORONARY HEART DISEASES

DRUG AND HORMONE THERAPY

There are presently no cures for atherosclerosis or coronary heart disease. However, there is reason to hope that the disease process is reversible and that therapeutic agents will eventually be found that will be able to cause regression of established atherosclerotic lesions and to restore health to diseased arteries. Meanwhile, with existing therapeutic measures, it may be possible to halt or slow down the progress of the disease and thus avert or delay the onset of such disabling or deadly manifestations as heart attacks. For heart-attack victims, the outlook for immediate and long-term survival has been improved by new concepts of intensive medical care, improved resuscitative measures, and anticoagulant therapy. Clot-dissolving agents such as urokinase may provide still other powerful weapons against coronary thrombosis and other thromboembolic complications of atherosclerosis. But our greatest hope for substantially reducing mortality from coronary heart disease lies in devising effective means of prevention.

THERAPEUTIC APPROACHES TO PREVENTION

Through epidemiological studies on many human populations, we have learned much about factors in the individual or in his environment that increase his risk of developing coronary heart disease. From this information has emerged

a highly useful portrait of the coronary-prone individual, a "coronary profile" that is helping physicians to spot the coronary candidate early and to initiate countermeasures that may reduce his risk and help to prolong his life.

Against some of these risk factors, the physician is helpless. For example, heart-disease risk increases steeply with age; is considerably higher for males than for females; and also appears to be higher for individuals with a strong family background of coronary heart disease, though conclusive evidence for this point is lacking. However, the physician can do something about most of the others, including the two most serious risk factors: elevated blood lipids and elevated blood pressure.

Elevated blood lipids.

The factor most consistently associated with increased susceptibility to coronary heart disease is elevated blood cholesterol. Excessive blood cholesterol levels may stem from certain metabolic disorders, such as hereditary hypercholesterolemia, hypothyroidism, or diabetes; but these are relatively uncommon causes. In most instances, moderate hyper-cholesterolemia can be traced to habitual dietary patterns. While switching over to a more prudent diet may be all that is required to correct many cases of mild to moderate hypercholesterolemia, many subjects may fail to respond to diet therapy. And, even at best, only relatively modest reductions in blood cholesterol can usually be expected from modifications that would not also produce major upheavels in habitual dietary patterns.

The limitations inherent in diet therapy have spurred research seeking drugs or hormones that might lower blood cholesterol safely and effectively by some direct action on processes involved in the absorption, synthesis, transport, or excretion of cholesterol by the body. The compounds that have been tested most extensively are nicotinic acid, estrogenic substances, thyroid hormones, and certain of their chemical analogs. Promising newcomers include CPIB ester (Ayerst) and cholestyramine.

Nicotinic acid, an inhibitor of cholesterol synthesis, usually brings about moderate reductions in blood cholesterol. Its effectiveness is enhanced when it is used in conjunction with diet therapy. Its toxicity appears to be relatively low. Although the drug produces flushing, gastrointestinal disturbances, or increased pigmentation of the skin in some patients, these side effects are seldom intolerable enough to force discontinuing the drug.

Estrogenic compounds may confer significant protection against recurrent heart attacks and increased long-term survival among middle-aged males who have previously suffered one or more heart attacks, the results of recent long-term studies indicate. In one study, estrogen therapy produced a very high incidence of feminizing side effects (breast enlargement, loss of sexual drive), but sharply reduced the incidence of recurrent heart attacks and increased five-year survival rates by 50 percent.

In the other study, significant protection was conferred by conjugated equine estrogens in doses that produced none of these undesirable side effects. Protection appeared to be greatest during the first 18 months, when mortality among estrogen-treated subjects was more than fifty percent lower than among controls. Thereafter, the effects were less spectacular; but, after three years, mortality in the estrogen-treated group was still one-third lower than that in the control group.

The findings of these studies suggest that middle-aged males, and possibly postmenopausal females who have overt heart disease or who appear to be coronary prone might derive substantial protection against first heart attacks or recurrent attacks from estrogen therapy. They further suggest that this protection need not entail intolerable side effects. However, more extensive scientific evaluation will be needed to settle the controversy concerning the place of estrogens in the prevention and clinical management of coronary heart disease.

Thyroid hormones lower blood cholesterol, but the doses required also raise metabolic rates; cause nervousness, tremors, and other signs of hyper-thyroidism; and very often cause angina pain in patients with coronary heart disease. Current research has been directed toward developing chemical analogs that will retain the cholesterol-lowering action of thyroid hormones, but produce fewer of the other metabolic effects. The most promising of the preparations developed thus far is D-thyroxine. In clinical trials with the compound, moderate reductions (15–25 percent) in blood cholesterol have been achieved. The drug is well tolerated by most patients, although increased heart rates, weight loss, angina, and other complications have occasionally attended its use.

CPIB Ester is a new drug that has shown great promise in clinical trials conducted to date. Not only does the drug reduce blood cholesterol, but it also produces even greater decreases in blood triglycerides, another lipid fraction strongly implicated in the development of coronary heart disease. There is some evidence that the drug also reduces the tendency of blood platelets to clump, and so it might confer some protection against certain of the thromboembolic complications of coronary heart disease that are so often responsible for its disabling or lethal consequences. Although no evidence of toxicity has been observed in short-term clinical studies, clinical experience with the drug has been too limited to predict whether it will retain its effectiveness and freedom from adverse side effects during long-term use.

Cholestyramine is a resin that combines with bile acids in the intestine to form a non-absorbable complex that is subsequently excreted in the feces. Bile acids are the major pathway of cholesterol excretion, but a substantial proportion of the bile acids derived from the oxidation of cholesterol are normally reabsorbed. By blocking this reabsorption step, cholestyramine stimulates increased bile-acid production by the liver at the expense of blood cholesterol. In most patients, the drug has reduced blood cholesterol levels by 15 percent or more. The drug itself is not absorbed from the gut and is non-toxic; but it is not pleasant to take, and large daily doses are required to reduce blood cholesterol significantly.

Neomycin and certain other antibiotics, when given orally, have brought about reductions in blood cholesterol comparable to those achieved wtih diet therapy or with other cholesterol-lowering agents. These drugs apparently increase the excretion of bile acids and bile salts, thereby causing additional cholesterol to be diverted for bile-acid production by the liver. The drugs may act by killing off normal bacterial inhabitants of the intenstine, which appear to be important in normal bile-acid metabolism even though their role has not been precisely defined. More recent evidence indicates that Neomycin also forms chemical complexes with bile acids, and so may act in a manner similar to cholestyramine. Diarrhea has been a common, though seldom serious side effect of Neomycin therapy.

The "combination of ingredients" approach to therapy, previously employed with considerable success in the treatment of hypertension, may also be applicable to the drug treatment of elevated blood lipids, recent NHI grantee studies suggest. Using CPIB and D-thyroxine separately, then in combination, the scientists found that the combination was more effective than either drug alone in reducing blood cohlesterol levels. CPIB alone reduced these levels by about 12 percent, D-thyroxine by 14 percent, but the combination achieved a reduction of 20 percent. CPIB also reduced blood triglycerides, but this effect was not enhanced when D-thyroxine was added.

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 that may be relatively common among Americans and that also appears to increase heart-disease risk. And it remains to be proved that lowering of serum lipid levels by any means—drugs or diet—affects incidence or mortality rates in coronary heart disease.

Data relevant to this question may be forthcoming from the Coronary Drug Study, a large-scale research project designed to assess the effects of various lipid-lowering drugs and hormones on heart-disease mortality among men aged 30–64 who have previously suffered one or more heart attacks. 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. Four drugs have been selected for this clinical trial: D-thyroxine, nicotinic acid, conjugated equine estrogens, and CPIB ester. These agents were chosen on the basis of their promising performance in earlier clinical trials and because they produce their lipid-lowering effects through different mechanisms.

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 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.

During the summer and fall of 1965 protocols for this far-reaching study were perfected, operational details were refined, and the first patients were actually enrolled in January 1966. In April 1966, 24 more clinics were admitted to the study. From these and the original four groups, it is expected that 2,000 patients will be enrolled by June 1967, by which time the minimum goal of 50 participating clinics should also be achieved. Heart Institute staff will engage in further recruitment to attract additional clinics, particularly from geographical areas or types of institutions not yet adequately represented.

The participating organizations are concentrated mostly in populous regimes. They range from the large medical centers to relatively 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, although it is hoped that more adequate representation may soon be achieved from the central and northwestern portions of the country.

Elevated blood pressure

Risk from 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 (Miltown, Wallace) may provide adequate blood-pressure control in very mild hypertension, especially if the patient is high strung or subjected to excessive pressure and tension in his job or family relationships.

Thiazide diuretics may also provide adequate blood-pressure control in many cases of mild hypertension. By promoting salt and water excretion, these agents tend to reduce blood and plasma volume. However, other evidence suggests that this is the only one facet of their action. They may also affect blood pressure by decreasing the sensitivity of smooth muscle in blood vessels to vasoconstrictive stimuli, but the mechanism underlying this effect has not yet been clarified. Thiazide diuretics also potentiate the blood-pressure effects of other hypotensive agents and are frequently employed in "combination of ingredients" therapy.

Reserpine and certain of its analogs, such as syrosingopine, are usually effective against mild to moderate hypertension, especially when used in combination with thiazide diuretics. These drugs reduce sympathetic 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 (Aldomet, Merck) is a very 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, Aldomet 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 (Eutonyl, Abbott), 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 looked bleak indeed.

Subsequent studies revealed that the fault lay, not in the inhibition of monoamine oxidase, but in the fact that 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 an MAO inhibitor of a new breed. 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 and antidepressant.

Guanethidine (Ismelin, CIBA) is an extremely potent hypotensive agent that is highly specific in its action. Like reserpine and methyl dopa, quanethidine 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 also 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 persistant 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 occurs. 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 automatic 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.

Coronary heart disease: clinical management

A new family of drugs that may prove highly effective in the clinical management of angina pectoris are *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 victims. Used alone or in combination with nitroglycerine, they have often enabled such patients to resume activities that formerly would have brought on disabling chest pain.

Acute heart attacks (myocardial infarction) usually result from the blockade of vital coronary arteries by blood clots. These clots may form on atherosclerotic lesions in diseased coronary arteries, especially in narrowed segments where the blood flows more slowly; or they may arise in larger blood 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 coronary thrombi or emboli. By preventing the growth or extension of the clot, anticoagulants may prevent it from completely obstructing a partially 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 infarctions, 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 properly and closely 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 cloths—either by attacking them directly or by activating the body's own clotlysing 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, not established fact; for the value of fibrinolytic therapy in the clinical management of coronary thrombosis has not been convincingly demonstrated.

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 bloodflow and heart-muscle salvage, investigators have had to rely heavily upon clinical impressions. The clinical course of myocardial infarction is too notoriously variable and unpredictable to inspire confidence in such impressions.

Further undermining confidence in the results of earlier clinical studies was the lack of suitability 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 definitive clinical studies now appear feasible. The fibrinolytic agent employed will be urokinase, derived from human urine. Urokinase is a "native" substance. Being non-antigenic it has a 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 also 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 undesirable side effects of earlier fibrinolytic agents.

Current NHI plans call for carefully controlled clinical studies using highly purified urokinase and standardized methodology at five cooperating institutions. Initially, the drug will be tested against peripheral vascular thrombosis and pulmonary embolism, but it is anticipated that the project will be expanded substantially to encompass definitive studies on the value of urokinase against coronary occulsion and certain strokes resulting from clots or emboli.

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 contraction. 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 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.

The third mechanism of death is the damage to the heart muscle resulting from the blockage of its arterial nourishment. This occurs to a greater or lesser extent in every heart attack. It is also one of the principal causes of the chronic disability, the shortness of breath, the pain accompanying effort, and other evidences of diminished heart function so frequently seen in patients who have recovered from one or more heart attacks. For these patients, drugs capable of providing continuous support to their failing circulation are essential for restoration to more normal living.

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 to the heart by electrical defibrillation equipment.

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 somewhat, 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 may be further diminished by the loss of normal blood-vessel tone. Widespread relaxation of blood vessels increases the capacity of the 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.

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 bloodflow may actually decrease.

In other instances of cardiogenic shock, there may be a widespread blood-vessel constriction rather than relaxation. This may sharply reduce heart output and systemic bloodflow 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 microspheres into the coronary circulation. Of animals developing cardiogenic shock, 85% died within 24 hours if untreated. But 75% 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 circulatory 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 heart 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 circulatory burden on the heart, or it may stem from the loss of functioning heart muscle tissue 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 serious and life-threatening complication. The 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.

Digitalis, used against congestive heart failure since 1785, is still the drug of choice, although crude digitalis preparations have been largely 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 if at all, 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.

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 losses 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 commerically 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.

Ethycrynic 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 or effectively combatting this massive and growing health problem resides in identifying and elminating 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.

ARTIFICIAL HEART PROGRAM

Mr. FLOOD. We also expressed our belief in the need for more activity aimed at the development of an artificial heart. We thought this should be pursued with extraordinary vigor. We have had testimony from some of the best people on this. How much do you have budgeted for 1967 and 1968?

Tell us about this.

Dr. FREDRICKSON. The budget in 1967 and 1968 remains the same.

Mr. FLOOD. You swept us off our feet on this for some years. Where are you now?

Dr. FREDRICKSON. The amount in the appropriation for 1967 is the same as the request in 1968 for $13.7 million. This is distributed, sir, between the activities of the two branches of this artificial heart pro-

gram which I described. This year roughly $7 million of that will be obligated in terms of contracts primarily for the development of assist devices, or toward the solution of problems that underlie the development of those devices.

Roughly $5.8 million will be obligated for the myocardial infarction centers or facilities that I described as being capabilities we want to develop within the next few years.

Dr. SHANNON. I would like to comment on the dollar level. This, again, is a program that we felt should be funded during the initial years at a substantially lower level than was advised by the National Advisory Heart Council. The figures for 1968 and 1967 are of our choosing. They are not the result of imposition of limitations by the Bureau of the Budget. It is our belief that, with the change in the directorship of the Herat Institute and the difficulties of getting the program off the ground, a substantial amount of the funds available this year—namely, somewhat more than $13 million—will be obligated quite late in this fiscal year. Any need for a substantial increase above the $13 million will be more perceivable by late next fall or prior to the 1969 budget. At that time we will have had the better part of a year's experience and be in a better position to project expenditures.

If things go as well as anticipated, there will be a substantial increase in the request for 1969. But we feel that the request for 1968 is very adequate to satisfy the urgent needs and fits very well with our own program for this activity.

RESEARCH PROJECTS

Mr. FLOOD. You are going to be able to finance 261 fewer research projects under the grant program in 1968 than in 1967. That is a reduction of over 10 percent. How is that going to affect your program? Is the need less? Are you getting fewer applications?

Dr. FREDRICKSON. I do not believe the need is less.

Mr. FLOOD. What is less?

Dr. SHANNON. Money.

FELLOWSHIP PROGRAM

Mr. FLOOD. I see you are not continuing the expansion rate of the fellowship program. You go from 201 to 179. Is that good?

Of course, it is not good.

Dr. SHANNON. Mr. Flood, as you pointed out, the overall budget increase was something less than 3 percent. The increased cost of doing business is substantially more than four percent.

These figures represent our best estimate of how we can distribute these funds in the most efficient fashion. They do not represent our desires or the research opportunity, but rather the stringency of the budget situation in which we find ourselves.

Mr. FLOOD. This is the two-edged sword. We beat you over the head about money and then all of a sudden run into an area in which we are interested especially. It works both ways, does it not?

Dr. SHANNON. Yes, sir.

TRAINING GRANTS

Mr. FLOOD. As we go on, it gets worse. In training you are cutting back the total program from 391 to 376. Again is the need for training decreasing?

Dr. FREDRICKSON. No, sir.

Mr. FLOOD. It couldn't possibly.

Dr. FREDRICKSON. No, sir.

Mr. FLOOD. What is the trouble?

Dr. FREDRICKSON. Money, sir.

Dr. SHANNON. I would point out a generalization that may have not been fully appreciated. The witness' primary presentation pointed out that this field is ready for a rather coordinated attack on a very complex problem.

Mr. FLOOD. That is, next fiscal year.

Dr. SHANNON. No, we talk about 5 years, sir. He said it was their belief, concurred in by the National Advisory Council, that there was a need to establish something like 10 complex cardiovascular research centers and that these would cost roughly $4 million a year.

I might say that to construct these centers will also cost about $4 million per center, $2 million of which will come from research facilities construction funds and $2 million from local sources, on balance. The implications of that plan are that he is projecting an activity, in terms of new resources, that in 5 years will be at the average of $40 million a year of new program content. If you translate that into scientific manpower, it means the full-time employment of something on the order of 700 well-trained scientists. This, then, has an impact on the mechanics by which we train such scientists. They will have to be derived from the training programs that are conducted by the Heart Institute at the present time.

However, that deferred expenditures must not be deferred too long, because if they are deferred too long they will materially impair the progress of the Institute. It is less important that they are deferred this year or perhaps even next year; but ultimately, if we are to have the knowledge we need, a large sizable bill will have to be paid.

DIRECT OPERATIONS

Mr. FLOOD. For direct operations you have an increase of about $3 million and nine positions. Why is this part of your program being treated so well? What is special about this part of your program?

Dr. FREDERICKSON. It is closer to me, but we are not biased in the distribution of the funds. Included in the needs for the direct operation are nine new positions as follows: First of all we need to get two technicians who can serve to run a program which will establish a colony of dogs to serve as blood donors.

Mr. FLOOD. Where are you going to get them?

Dr. FREDRICKSON. We can get the dogs.

Mr. FLOOD. I mean the technicians.

Dr. FREDRICKSON. I think we will be able to find them, if we have the funds to support them.

Mr. FLOOD. You are not going to be dognappers, I suppose?

Dr. FREDRICKSON. No, sir.

Dr. SHANNON. We never have, sir.

Dr. FREDRICKSON. One reason we need this program is that the cost of dogs is rising astronomically. In cost accounting terms, the cost of dogs at NIH, of which the Heart Institute uses 80 to 90 percent, will increase from about $27 per dog to $120 this year. In order to cut back

and to effect a saving we want to try to reuse dogs as a source of blood.

Mr. FLOOD. What kind of technicians are those?

Dr. FREDRICKSON. These will be good dog handlers who can carefully take care of animals, bleed them, and so on.

Mr. FLOOD. You have seven more?

Dr. FREDRICKSON. The other seven positions include three scientists and four technicians who will allow us to outfit and man some newly assigned space which we are going to be able to get next year. We have needed it for a long time. Half a wing will be open to us, available from the displacement of the old library at NIH.

Mr. FLOOD. That is the people. What about the money, $3 million.

Dr. SHANNON. There are a number of things here that do not really appear. There is the need to absorb salary increases within the total budget. There is the need to absorb increased costs. The bulk of these dollars will go for those purposes rather than for new programs. On the other hand, this $3 million was approved by us, at the NIH level, because it was our conviction that the direct operation of the Heart Institute was not supporting its scientists, in terms of materials and equipment purchases, so as to get the maximum benefit out of well established scientists who have extraordinary ability. This increase tends to redress the inadequate support they have had in the last 3 or 4 years. There are mandatory increases contained within the $3 million. The remainder is for either the functions, as defined by the Director, or to redress what had developed into unhealthy, inadequate support for some of the senior scientists.

HEMOPHILIA

Mr. FLOOD. Do you want to say something about hemophilia?

Dr. FREDRICKSON. Yes. May I interject that in the $3 million just referred to, is also $1.1 million for the national blood program for next year. That is part of the increase under "Direct operations."

Sir, hemophilia, as you know, is an inheritable disorder or disorders which cause people to bleed. There are about 100,000 so-called bleeders in the United States. Of these, although we do not know the exact figure, probably half——

Mr. FLOOD. What does a dentist do if he has one of these people; what do you do about it?

Dr. FREDRICKSON. He transfers that patient immediately to the hands of a capable hematologist, who, on ascertaining that this patient is a hemophiliac—that is, by definition, misses one of these blood fractions——

Mr. FLOOD. I would presume he would advise the dentist beforehand.

Dr. FREDRICKSON. I am sure he would, because it would have been expressed before he got to the dentist.

Mr. FLOOD. You have a special place to take these people. You say 100,000.

Dr. FREDRICKSON. Of these 100,000 people who bleed——

Mr. FLOOD. Is that a lot?

Dr. FREDRICKSON. It is an awful lot when you consider the cost per hemophiliac, sir. About 50,000 of these bleeders are hemophiliacs and 90 percent of these, in turn, have classical hemophilia. There are another 10 percent that have a so-called Christmas disease.

Mr. FLOOD. How is this transmitted, through the male line?

Dr. FREDRICKSON. Yes; it is a sex-linked transmission. It is actually transmitted through the female but only the males will express the effects.

Mr. FLOOD. By generation or will it skip? Will it skip a few or what?

Dr. FREDRICKSON. It is very predictable. A female carrier will affect half of her sons and she will transmit to half of her daughters the ability to be a carrier.

The only treatment for hemophilia is antihemophilic globulin, which is relatively unstable. It does not stay around unless you use fresh blood. And a hemophiliac may require as much as 200 units of blood during a severe hemorrhagic crises.

Mr. FLOOD. What is the life expectancy of these people?

Dr. FREDRICKSON. The left expectancy is changing.

GEOGRAPHIC DISTRIBUTION OF HEART ATTACKS

Mr. FLOOD. Do you have a geographic difference in heart attacks?

Dr. FREDRICKSON. In the United States?

Mr. FLOOD. Yes; in the United States.

Dr. FREDRICKSON. There is not a serious difference in distribution. A number of studies have shown that different areas will have different attack rates but this may be due to a number of factors. There is not a major difference in various parts of the country.

Mr. FLOOD. There is not?

Dr. FREDRICKSON. No, sir.

Mr. FLOOD. Mr. Laird.

HISTORY OF BUDGET REQUEST FOR NATIONAL HEART INSTITUTE

Mr. LAIRD. You requested of the Public Health Service $208,779,000 for the National Heart Institute for 1968. Is that not correct?

Dr. FREDERICKSON. That is correct.

Mr. LAIRD. And the Public Health Service approved $194,796,000. What are the major items that were eliminated by the Public Health Service?

Dr. FREDRICKSON. Mr. Laird, I did not participate in any of the development of that budget and I cannot answer your question with any authority.

Mr. FLOOD. Cannot your men here answer it?

Mr. HENSCHEL. The artificial heart program took the greatest cut.

Mr. LAIRD. Which amounted to $14 million?

Mr. HENSCHEL. No. There was a $12 million reduction in research grants and $1.1 million reduction in the artificial heart program.

Mr. LAIRD. So the largest reduction was in the research grants in the extramural research program?

Dr. FREDRICKSON. Yes.

Mr. LAIRD. In the Department's submission to the Bureau of the Budget there was a $4 million reduction. Where was that $4 million cut made?

Dr. SHANNON. That is made up of a $4 million increase in one item and a reduction of $8 million in another.

Mr. LAIRD. What are they?

Mr. HENSCHEL. Again, the artificial heart program was increased by the Department and the decrease was in research grants.

Mr. LAIRD. The artificial heart program was increased by $4 million and there was a decrease in research grants by $8 million?

Mr. HENSCHEL. That is correct.

Mr. LAIRD. For a total net reduction in research grants of $20 million?

Mr. CARDWELL. $22,431,000, to be exact.

Mr. LAIRD. Now we get down to the President's budget which is $167,954,000. You already had a net decrease of $18 million from the reviews by the Public Health Service and the Department of Health, Education, and Welfare, and a $22 million reduction in the area of the extramural research grant program. Will you explain to me this additional reduction in the President's budget of approximately $22 or $23 million?

Mr. HENSCHEL. An additional $14 million was cut from the extramural research program for grants.

Mr. LAIRD. We have a reduction of $22 million and another of $14 million for a $36 million reduction in grants. Is that correct?

Mr. HENSCHEL. In the artificial heart program, again, there was a $7 million reduction.

HISTORY OF BUDGET REQUEST FOR ARTIFICIAL HEART PROGRAM

Mr. LAIRD. A $7 million reduction in the artificial heart program? You must have requested $20 million, then?

Mr. HENSCHEL. Yes.

Mr. LAIRD. And it was reduced to $13 million?

Mr. HENSCHEL. Yes.

Mr. LAIRD. What else?

Mr. HENSCHEL. The others were small but the total reduction was $7.8 million.

Dr. SHANNON. I would like to comment on one part of that reduction, the artificial heart program. At the time we forwarded the request from the National Institutes of Health to the Public Health Service and they forwarded it to the Department, we said that we were not, at that time, able to give a firm figure as to the needs of the artificial heart program. So this more or less floated until a determination was made by the Department of Health, Education, and Welfare and the amount was reduced from $20 million to $13.5 million. This reduction was made on our recommendation because, by that time, we had completed an assessment of the program and we felt that the proposed figure, that finally went from the Department to the Bureau of the Budget, was, indeed, the maximum amount that was needed. So that it would be difficult for me to quarrel with the changes between the initial submission and the final allowance.

Mr. LAIRD. So in the artificial heart program there was no conflict between the Department of Health, Education, and Welfare, the National Institutes of Health, and the Bureau of the Budget?

Dr. SHANNON. That is correct.

Mr. LAIRD. You are in complete agreement that there are sufficient funds provided in this budget for the artificial heart program?

Dr. SHANNON. That is correct, sir.

Mr. LAIRD. And if there is any problem involved it is one of overestimating rather than underestimating in this program?

Dr. SHANNON. No, sir. I think this is a very realistic figure. As I said, there was a slippage in the program due to the change of leadership in the Institute. We feel this is a very realistic figure.

Mr. LAIRD. So the only thing in dispute between the Heart Institute and the National Institutes of Health and the President's budget request is approximately $36 million in extramural research grants. That is the difference between your original submisison and the figure before this committee.

Dr. SHANNON. Yes, sir.

TRAINEESHIPS

Mr. LAIRD. There has been no reduction, then, as far as the traineeships?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. I cannot see this developing in these figures. I thought there would be some mention of traineeships.

Mr. CARDWELL. May I make a comment? The data I have only trace reductions from the submission by the Surgeon General and the only item that would affect training there is one reduction made by the Bureau of the Budget of $705,000. So I could assume that the remaining reduction occurred between the submission by the Director of the National Institutes of Health, the submission for the Surgeon General to the Secretary.

Mr. LAIRD. There is a $194 million submission to the Department and there is only a $705,000 difference in the area of traineeships. Is that correct?

Mr. CARDWELL. That seems to be right, sir.

Mr. LAIRD. So it is a relatively minor item?

Mr. FLOOD. You mean for NIH?

Mr. LAIRD. The Heart Institute.

Mr. CARDWELL. It would appear from the record that the National Institutes of Health made their own distribution between training and other programs.

Dr. SHANNON. May I clarify that, Mr. Laird?

The primary difference is the estimate of the need for research grants at different levels. I might say the Heart Institute asked for more for the training program than we allowed.

Mr. LAIRD. How much did you allow?

Dr. SHANNON. We allowed roughly what we felt was an increased-cost-of-doing-business type of allowance. We felt that the primary push this year should be in the establishment of cardiovascular research centers. This was reflected in the substantial increase proposed for research grants. Our judgments were made within what we figured to be reasonable expectations and reasonable overall program increases and we felt that their need for research grants was substantially greater, at that particular point of time, than the need for additional training grants. This was a judgment made Institute by Institute and I think comparable tables will show that in some of the Institutes we recommended substantial increases in training grants but in most Institutes the major thrust this year was in the research grant area.

Dr. FREDRICKSON. Sir, there are two center items that appear in the budget. First we have categorical clinical centers.

Mr. LAIRD. I am talking about the cardiovascular research centers.

Dr. FREDRICKSON. These are represented by the figure $800,000 for the years 1967 and 1966 and the item also appears in 1968. This $800,000 is solely for planning grants; awards made to institutions to plan for possible centers.

Mr. LAIRD. We started planning in 1966.

Dr. FREDRICKSON. We started awarding planning grants in 1966.

Mr. LAIRD. What has come of these? We have been making these planning grants. Where are the centers that came about after these planning grants were made?

Dr. FREDRICKSON. No centers have yet been established, sir.

Mr. LAIRD. No centers have yet been established?

Dr. FREDRICKSON. No, sir.

Mr. LAIRD. We have been making these planning grants for a long time.

Dr. SHANNON. Mr. Laird, it seems a long time. In the initial year, 1966, you may recall, we made a presentation to this committee in respect to additional funds needed to carry out the major recommendations in the report of the Heart, Cancer, and Stroke Commission. In that report it was said that planning funds were needed for the Cancer Institute and the Heart Institute to achieve better geographic distribution, and an appropriation was made. While it seems a long time, I would point out that the appropriated funds were released, by the apportionment process, late in the fall, so we had about 6 months to complete the planning operations. This was hardly enough time for us to make a commitment for a program which would cost nearly $40 million a year to run. So in the 1967 appropriation the final phase was to continue——

Mr. LAIRD. How many grants did you make in 1966?

Dr. FREDRICKSON. We made six in 1966.

Mr. LAIRD. Six in 1966 and how many in 1967?

Dr. FREDRICKSON. Four.

Mr. LAIRD. So you have had 10 that have been funded already?

Dr. FREDRICKSON. Yes, sir.

Mr. LAIRD. When will the planning period be over with these 10?

Dr. SHANNON. The time figured now is that it will be over shortly.

STATUS OF PLANNING

Mr. LAIRD. Have those who received grants in 1966 finished their planning?

Dr. SHANNON. I believe so.

Dr. FREDRICKSON. Some in the earlier group have practically completed their planning.

Mr. LAIRD. Where are they?

Dr. SHANNON. The point I would make is that planning in these centers involves defining the program, the facilities for the program, the private contributions to provide matching funds for physical facilities, and finally a grant to the Institute. These planning grants became available about 16 months ago. I think some are ready to submit their proposals for the establishment of such a center.

Mr. LAIRD. Some have already moved forward, then?

Dr. SHANNON. Yes, indeed.

Mr. LAIRD. Let us go through each of these.

Dr. FREDRICKSON. Mr. Laird, may we submit the list for the record?

Mr. FLOOD. Has not planning been going on 18 months?

Dr. SHANNON. No. The apportionment was made the first week in November.

Mr. LAIRD. You do not have available the 10?

Dr. FREDERICKSON. No, sir.

Mr. LAIRD. There may be four or five where the planning is all done?

Dr. FREDERICKSON. None of the institutions that have had planning grants have submitted operational plans but some are very close to that stage and we have been firming up this definition so we might match the operational requests.

Mr. LAIRD. The idea was this would be an additional emphasis and an additional incentive to enlarge this type of work.

Dr. SHANNON. This is true, one has to have the beginning of scientific excellence for a program of this sort. It is possible to expand, using a wide variety of techniques, this core staff in anticipation of expanding resources. It would be unwise to have the planning done in such a way that only after the facility was completed would we begin to develop programs. But this is for programs not in existence at this time but being built around a core of excellence that has been built over a period of time.

Mr. LAIRD. These 10 you are talking about are not included in those already in existence?

Dr. FREDERICKSON. They are not included in this definition but they may qualify for such awards. Some are so far along they may be able to come in with operational grant requests very soon.

Mr. LAIRD. Are these all in connection with medical institutions, medical schools?

Dr. FREDRICKSON. At the present time I believe all those that have planning grants, certainly the majority of those that we would expect to become centers, are in association with major medical centers.

CLINICAL TRAINING GRANT PROGRAM

Mr. LAIRD. What about the clinical training grant programs? Are they all in connection with medical schools? You embarked on a new clinical training program, I believe, in 1966?

Dr. FREDRICKSON. Yes; $1 million in fiscal 1966, and this year we have 27 grants to 26 institutions. Most of these are in university centers.

Mr. LAIRD. You must have $10 million to $15 million you will be approving between now and the first of July that has not been allocated for your grant program. Is that correct?

Dr. FREDRICKSON. We have the obligations as of February 28.

Mr. LAIRD. Is any of this in the clinical training grant program?

Dr. FREDRICKSON. We have in the training area a total of about $14 million still to be obligated as of last February 28, and I believe some of these are in the clinical training area, sir. Yes; they are.

Dr. SHANNON. I would point out that this is a deceptive figure because the bulk of these funds is for already existing training activities. The total for training is $18.4 million and most of it is obligated in the last quarter. So that the $14 million of unobligated funds does not constitute a sum available for activities which have not been programmed.

OPERATIONAL BACKLOG REPRESENTED BY PLANNING GRANTS

Mr. LAIRD. We are going ahead, though, and making more planning grants this year?

Dr. FREDRICKSON. Yes, we are.

Mr. LAIRD. And it seems to me we are making a lot of planning grants, one on top of each other. We find ourselves in a position where we are building up a tremendous operational backlog here. You already have 10 or 11. How many will you grant this year?

Dr. FREDRICKSON. Six were granted last year.

Mr. LAIRD. And four the year before. How many will you grant this year? I will bet you will end up with six or seven this year and be up to the twenties in 1968.

Dr. FREDRICKSON. The two already awarded in 1967 and two others that are pending bring the total to 10 and we expect to award at least two to six during fiscal 1968.

Mr. LAIRD. I would like to develop the figure on what your backlog will be when you get into the operational area. It is fine to keep on making these planning grants but what will the operation cost be?

Dr. SHANNON. I gave you a figure for 1966 and 1967.

Mr. LAIRD. You gave us a figure of $40 million for the 10. If they were approved it would be $40 million. That is for planning grants funded in 1966 and 1967. What would happen if we gave more planning grant funds in 1968?

ADEQUATE NUMBER OF CARDIOVASCULAR RESEARCH CENTERS

Dr. SHANNON. When this program was started, considering the population distribution and considering the needs of the already established programs upon which these centers could be based, it was calculated that roughly 12 such centers would give each area of the country a good program. This was the base figure that was used. We do not expect that every area that is given a planning grant will, in fact, become operational, and certainly this will not be automatic. So, if we are going to get some 10 to 12 out of the aggregate, it is highly likely that we should provide planning grants for as many as 15 or 16. These planning grants are not losses if they do not get the operational grant. They will have substantially increased their capability. So I think we should plan to have more planning grants to provide free competition among the ones who are funded. Only in this way can we be assured of excellence, on the one hand, and geographic distribution on the other.

GEOGRAPHICAL DISTRIBUTION OF CENTERS

Mr. LAIRD. What about this geographic distribution? I would like to find out the kind of geographic distribution you have on the first six and these four.

Dr. FREDRICKSON. May I speak to that?

I have a list of six of the 10. For clarification, four of these were actually awarded in 1966 and six in 1967. The four in 1966 were awarded practically the last month of the year and they will not be completed until 1968. They are for a 2-year planning phase.

Mr. LAIRD. This fiscal year we are considering now?

Dr. FREDRICKSON. That is right. Of six of these 10 planning grants, the first four were awarded to the Presbyterian Medical Center in San Francisco, the University Hospital at Boston, Indiana University, and the University of Alabama. The remaining two of the six are at Seattle, the University of Washington, and at Salt Lake City, the University of Utah. And I will provide the other four planning grants when we get them.

Mr. LAIRD. How many applications for planning grants do you presently have?

Dr. FREDRICKSON. Unfunded?

Mr. LAIRD. Yes; unfunded.

Dr. FREDRICKSON. We do not have that with us, sir.

ANNUAL COSTS OF OPERATIONAL GRANTS

Mr. LAIRD. Could you give me an estimate of those? I am trying to find out what operational costs we are really committing ourselves to in this program. This is the time for us to develop that and find out exactly what our cost picture will be for the next few years. There is no use funding these planning grants unless we also fund some operational activities at a later date.

Dr. FREDRICKSON. We would certainly expect to come in and ask for funds for operational grants in 1969. The number of awards we would anticipate will depend on an analysis of the planning grants. We had planned to award one or two operational grants in 1969 so that we might progressively implement this program.

Dr. SHANNON. But the overall rate here will involve, roughly, $20 million for facility construction, assuming 50–50 matching, and approximately $40 million a year operational cost. This would be for 10 units, approximately $4 million apiece. That is a very realistic figure.

Mr. LAIRD. How will these centers be tuned in on the heart, cancer, and stroke program? Here we are talking about actual research activities as compared with specialized types of care for individuals in an area.

Dr. FREDRICKSON. A very major share of the research activities of these cardiovascular research training centers deal with clinical research and we are sure in this environment there will be unusual opportunity for the training of individuals in the most advanced techniques of cardiovascular diagnosis and therapy. These will very materially affect the quality of care of patients with cardiovascular disease. These centers will have national or even international scope and reputation but will also have a very important effect on the regions in which they are located.

Mr. FLOOD. Will these all be M.D.'s?

Dr. FREDRICKSON. We would expect them to include both doctors of medicine and those holding degrees in related sciences.

Mr. LAIRD. Why could not these be coordinated with the regional program?

Dr. FREDRICKSON. In the definition of centers that we are insisting upon as much as we can, there is a degree of breadth and excellence required that could not presently be uniformly achieved on a regional distribution basis.

Mr. FLOOD. Mr. Laird asked the key question. Tell us about this regional business. Is my heart, cancer, and stroke program in Philadelphia a part of what you are talking about, too?

Mr. LAIRD. It really should be.

Dr. SHANNON. There will be in round figures—I do not know the precise number—by next October roughly 50 regions or regional medical programs spread across the Nation that probably have the potential of covering 90 to 95 percent of the population.

Mr. LAIRD. You are awfully optimistic.

Dr. SHANNON. I am talking primarily of the present phase.

Mr. LAIRD. You mean you will be thinking about that?

Dr. SHANNON. Grants will have been made for planning purposes, period.

We have 50-odd regions. Now we are talking about 10 cardiovascular research centers giving a broad geographic distribution.

Mr. FLOOD. Are you back to Mr. Laird's question about the regions?

DIFFERENCE BETWEEN REGIONAL MEDICAL PROGRAM AND CARDIOVASCULAR CENTERS PROGRAM

Dr. SHANNON. Let me give you the difference between the regional medical program and the cardiovascular centers. The cardiovascular centers are there to develop the most advanced techniques for the treatment and prevention of disease which will then be available to all centers and including those in the regional program. But the coupling will not be between the regional programs and the cardiovascular centers because the numbers will not match. But this is the way to undertake highly scientific research. Now, on the other hand, they will have a substantial impact on the quality of the staffing in the university hospitals and associated areas within which they are located, which is the primary purpose of aiming for geographical distribution. They will have an impact on training, particularly of clinical people.

Mr. FLOOD. Are you going to consult the medical people, the hospital people, or just give them a fait accompli? Will you talk to the people in the provinces?

Dr. SHANNON. We are not talking to people in the provinces on this particular program, though each of the groups is well aware of our attempt to develop these highly sophisticated undertakings and they are looking forward to having their staffs trained to supplement their needs and in some cases to refer specific case material to them.

Mr. Flood, you may recall——

Mr. FLOOD. This is Mr. Laird's question about the regions.

Dr. SHANNON. You may recall we talked about how to handle the problem of choriocarcinoma. We said the patients require specialized therapy. There are about 5,000 a year. The unit we intend to establish to handle these cases will not be organized on a regional basis. They will be organized on a geographic basis, but they still will constitute a resource for the regional program. So we are dealing here with re-

sources which go beyond the limits of geographic regions. In this case the coupling is loose and not direct.

Mr. LAIRD. If there is one thing demonstrated by the war in Vietnam it is that modern transportation will make very expensive equipment and expert medical services available to those who need is very quickly even though they are long distances away. This will change the whole outlook of service to people, I think. When we are talking about 10 regions, for instance, it seems to me from a practical standpoint that this has to be tied in with the treatment of patients in the heart, cancer, and stroke program. You will have a concentration of specialists in these regions and you will be in a position where you will be transporting people in this country for medical services as we never have before.

Dr. SHANNON. When the question came up of where the regional medical program should be assigned, it was our conviction that, if it were assigned other than to the National Institutes of Health, we would have a monstrosity. The same universities that have these advanced capabilities will serve as the basis for the extension of that knowledge into the community. If one were to attempt to divide that administrative responsibiilty between two groups, it would destroy the program. We felt that NIH was the only logical repository for such a program.

Mr. LAIRD. We are really talking about an expenditure during the decade of the seventies of over $1 billion. Is that correct?

Dr. SHANNON. I think so; yes.

PROJECTED EXPENDITURE ON HEART CENTERS

Mr. LAIRD. And in the heart area alone, beginning with the 1969 fiscal year budget, it will be about $40 million for the 10 centers?

Dr. SHANNON. By 1971 or 1972, sir.

Mr. LAIRD. What do you think operational grants will be in the 1970 budget?

Dr. SHANNON. Our estimate is that in 1969 we would like to get not less than two or three underway. I would expect that to be a very small downpayment. That will be in the order of 1 or 2 or 3 million.

Mr. LAIRD. Plus your construction?

Dr. SHANNON. I would cover that in another account. Over the short run the cost of these will not be great but they will be extended over a subsequent 2- or 3-year program. In 1969, I would think it would be substantially below $10 million.

Mr. LAIRD. I wish you would amplify on this testimony and give us some more definite cost figures for the record.

(The information follows:)

NHI CARDIOVASCULAR RESEARCH AND TRAINING CENTER PROGRAM

A cardiovascular research and training center is defined as an organizational unit established within a university or other institution for the broad purpose of conducting research on cardiovascular disease problems. It should be staffed with a corps of scientists capable of creative and independent research, organized under outstanding leadership, and oriented to highly original investigation and to the postgraduate training of scientists in many disciplines.

The research program of the center will be deeply involved with a spectrum of cardiovascular-disease problems whose solutions require the collective talents of individuals from the various disciplines of clinical medicine and also from the biological, engineering, physical, and social sciences. It will include clinical and non-clinical investigations in depth, using a broad range of scientific methods. It should provide for research staff members to work in sufficiently close proximity with one another and with sufficient integration of their activities so that ideas and technical advances can be continuously exchanged, and critically evaluated and research opportunities quickly recognized and exploited. Of prime concern will be the inter-relation of laboratory and clinical research so that problems of human disease receive optimal attention. The center should provide, or be closely allied with, personnel and facilities essential to the conduct of sophisticated diagnostic and therapeutic procedures.

The center should provide an especially favorable environment for training scientists specializing in cardiovascular-disease research. It should be able to attract high-quality trainees representing a number of disciplines and to equip them with the finest skills and techniques that modern biomedical research can provide.

The center concept also offers funding advantages not provided by a loose aggregation of individual research grants. Greater efficiency in the administration and use of grant funds can be achieved and specialized equipment, facilities, and other resources provided with the greatest economy. Moreover, the sustained high level of excellence and productivity of such centers will justify support of greater stability and continuity.

The cardiovascular research and training center grant will allow for the inclusion of funds for the care of research patients on both an inpatient and an outpatient basis, for alteration and renovation of existing space, for salaries of all categories of personnel, for the purchase of equipment and supplies, and for other expenses as may be needed to support the research and training program of the center. If funds for the construction of physical facilities to house the center are to be requested from the Public Health Service, the application for these funds should be reviewed as an *integral* part of the cardiovascular research and training center grant proposal.

Chronology of Approach

The precise sequence of steps necessary to accomplish the goals of this program will differ in specific instances, depending on the current status of cardiovascular research and training at an applicant institution. The following overall approach will be generally applicable:

Planning phase.—During this period the institution will develop detailed plans for the center. The planning activity may include, for example, definition of the organizational structure for the proposed center *within* the framework of the existing (parent) institution; definition of the program objectives in research and in training, and the relationship of these to the existing, or proposed post-graduate research and clinical care activities of the institution; definition of the managerial and administrative arrangements necessary to implement and maintain a cardiovascular research and training program of a high order of excellence; and definition of the physical facilities required to house the center activities.

It is anticipated that this planning phase will require one to two years in most instances. NHI is funding these planning activities through grants for the express purpose of *planning the development of a cardiovascular research and training center.* As of April, 1967, NHI has awarded planning grants to 7 institutions: 1) The University of Washington, 2) the University of Utah, 3) Presbyterian Medical Center (San Francisco), 4) University of Alabama, 5) University Hospital (Boston), 6) Indiana University, and 7) Ohio State University. An additional grant, to Duke University, has been approved; and two others, to the University of Minnesota and John Hopkins University, will be reviewed at the June, 1967 meeting of the National Advisory Heart Council.

Selection of planning grant awardees is determined competitively on the basis of an institutional proposal to plan a center in keeping with the purposes of this program. The institutions are duly informed, however, that the award of funds for planning does not constitute a commitment for subsequent funding of an operational activity.

When an institution has prepared a plan for the development of a center, it is expected that implementation will be sought in two successive stages, described below.

"Pilot" Operational Stage.—Soon after the conclusion of the planning period, most applicants will request relatively modest operational support for the center activity and, if required, support for the alteration and renovation or construction of physical facilities to house the program. This transitional period between planning and full-scale operation will probably require three to seven years. Three years is optimistically considered the minimum time needed to develop a program if the construction of new physical facilities is not required. The seven year time period allows approximately one year for the review and approval of an application for funds for construction, three years for actual construction, and three years for recruitment and development of full operations. The Institute and Division of Research Facilities & Resources will arrange for coordination of the review and approval of applications for construction funds with the review and approval of operational grant (center grant) applications.

During the transitional period the operational grant will provide support by consolidating research and training activities previously supported through individual grants. It will also provide funds for central facilities and for new program development as the availability of space and manpower permit. In this early phase, the funding requirements for eventual full-scale operation cannot be accurately projected or assessed; therefore, applicants will be encouraged to request supplemental support as their center program develops.

Full Operational Stage.—The transition between pilot and full operational phases will probably occur four to nine years following the initiation of planning. Thus, this will allow one to two years for planning and three to seven years for program implementation. When the center is fully operational, the major source of support for the research and training activities of the center will be provided by an NHI center grant. However, this will not preclude the awarding of other research grants from NHI and from other divisions of PHS to support some activities of the center. However, the total PHS support should be coordinated centrally by NHI.

Current status of the program.

To date NHI has awarded or approved 8 center planning grants with 2 others pending. We expect that the need for planning funds will continue at least through fiscal year 1969 at the level of approximately $800,000 per year. A total of 20 awards will eventually be funded in order to provide an adequate base for selecting, on the basis of competitive review, approximately 12 recipients for operational grants. At least one prototype of the cardiovascular research and training center has been developed without the need for a formal planning grant. This center is currently funded through an NHI program project grant. NHI would propose to convert the support device for this program to a center grant beginning with FY 1969, or earlier if funds are available.

If the first operational funds were available in 1968, the Institute's projection for future growth of this program, based upon centers in full or in partial operation, would be in the following sequence: 1 in 1968; 2 in 1969; 5 in 1970; 7 in 1971; 10 in 1972; and 12 in 1973. This allows for carefully planned development of a realistic number of true centers of excellence. When fully operational, the annual budget for each center is estimated at approximately $4 million.

Although the activities of these centers will be national or international in scope, they will doubtless exert a strong and beneficial influence on cardiovascular research and clinical care in the communities and regions in which they are located. In time, enough institutions should develop the capabilities for meeting the stringent qualifications for center status to provide a broad geographical distribution.

Planning grants for NHI Cardiovascular Research and Training Centers

I. GRANTS AWARDED

Grant No.	Principal investigator	Institution	Starting date	Amount (direct costs only)			
				Fiscal year 1966	Fiscal year 1967	Fiscal year 1968	Fiscal year 1969
HE 10687	Dr. John R. Hogness.	University of Washington.	Jan. 1, 1967	--------	$101,306	$25,428	-------
HE 10688	Dr. Alexander Schmidt.	University of Utah..	-----do--------	--------	49,288	36,800	-------
HE 10690	Dr. Frank Gerbode..	Presbyterian Medical Center, San Francisco.	June 1, 1966	$41,800	40,300	--------	-------
HE 10691	Dr. T. JosephReeves.	University of Alabama.	-----do--------	160,480	54,966	--------	-------
HE 10692	Dr. Robert W. Wilkins.	University Hospital, Boston.	-----do--------	25,106	24,818	--------	-------
HE 10693	Dr. James B. Hickam.	Indiana University.	-----do--------	76,500	75,400	--------	-------
HE 11036	Dr. James V. Warren.	Ohio State University.	Jan. 1, 1967	--------	58,748	58,149	-------
II. APPROVED, TO BE AWARDED							
HE 11308	Dr. Robert E. Whalen.	Duke University....	May 1, 1967	--------	81,932	116,350	-------
III. PENDING JUNE, 1967 COUNCIL							
HE 11459	Dr. Richard L. Varco.	University of Minnesota.	July 1, 1967	--------	--------	[1] 61,104	$82,000
HE 11464	Dr. E. Cowles Andrus.	Johns Hopkins University.	-----do--------	--------	--------	[1] 64,228	65,638

[1] If approved, probably will be paid from fiscal year 1967 funds.

Mr. LAIRD. That is all.

Mr. FLOOD. Mr. Natcher.

GROWTH OF BUDGET FOR NATIONAL HEART INSTITUTE

Mr. NATCHER. Dr. Fredrickson, your increase for 1968 over 1967 is $4,293,000. Do you need this amount, Doctor.

Dr. FREDRICKSON. Yes we do, sir.

Mr. NATCHER. All of it?

Dr. FREDRICKSON. Yes.

Mr. NATCHER. Starting back in 1958, according to your justifications under the National Heart Institute, for the fiscal year 1958 I believe you had a total of $36,083,000 for the regular fiscal year which included the pay act cost. Now it has gone up from 1958 to your request for 1968 of $167,954,000.

Dr. FREDRICKSON. Yes, sir.

Mr. NATCHER. That is quite an increase, is it not, Doctor?

Dr. FREDRICKSON. Yes, it is, sir.

Mr. NATCHER. Is all of it justified?

Dr. FREDRICKSON. I think so, yes, sir.

Mr. NATCHER. In answer to one of the Chairman's questions you talked about Christmas disease. What is that?

Dr. FREDRICKSON. This is a disease which is one of the hemophilias. About 10 percent of all hemophiliacs have Christmas disease and it is due to an inherited deficiency of a blood clotting factor known as factor IX.

Mr. NATCHER. You call it Christmas disease?

Dr. FREDRICKSON. Yes. That was the name of the first patient.

CRITERIA FOR AWARDING CONTRACTS FOR RESEARCH

Mr. NATCHER. In your statement to the committee you mentioned your contracts for further research and development, and so forth. Doctor, in awarding a contract what do you keep in mind as far as the National Heart Institute is concerned? What do you consider?

Dr. FREDRICKSON. We consider several things, sir. The first is the relevance of the contract to the program. We request proposals that will lead to the acquisition of the information we want. Therefore the relevance of the proposals to that specific request is the primary consideration.

The second consideration is the quality of the proposal. Here we are dealing, and hope always to deal, in a highly competiitve situation that will assure the best quality that is available.

These, I think, are the two prime factors.

Mr. NATCHER. Thank you.

Mr. FLOOD. Mr. Michel.

DEATH RATE DUE TO CARDIOVASCULAR DISEASE

Mr. MICHEL. Doctor, what is the rate of death due to cardiovascular disease in this country?

Dr. FREDRICKSON. Approximately 1 million deaths occurred in 1965 from cardiovascular disease. The death rate for cardiovascular disease then was 516 per 100,000, sir.

HEART RESEARCH ACTIVITIES IN PRIVATE SECTOR

Mr. MICHEL. Are there any estimates or sound figures of money expenditures by the private sector to do what we have been talking about here so far as the Federal Government activities?

Dr. FREDRICKSON. Yes. The last best estimate was made by the President's Commission on Heart, Cancer, and Stroke for 1963. It was estimated at that time that approximately 70 percent of the cardiovascular research support came from the National Heart Institute; another 10 percent from the Government; and the remainder from the private sector.

Mr. MICHEL. That was when?

Dr. FREDRICKSON. That was in the year 1963, sir. And the total amount was estimated to be approximately $122 million.

Mr. MICHEL. Do you have any figures before that year, 5 or 10 years before?

Dr. FREDRICKSON. We do not have figures except for the year preceding 1963. There was a moderate increase in the amount, sir.

Mr. MICHEL. What is the breakdown of the figures in this year, 1967?

Dr. FREDRICKSON. My estimate is that the percentages probably are fairly similar. This is a very rough estimate. This country is spending approximately $200 million now on cardiovascular research. Next to the Heart Institute, the largest single agency supporting cardiovascular research is the American Heart Association, with a current research budget of approximately $11.5 million.

Mr. MICHEL. Is that for the current year?

Dr. FREDRICKSON. Yes.

Mr. MICHEL. Is that an increase over the last several years?

Dr. FREDRICKSON. I believe it is an increase. We know that in 1963 the American Heart Association's research budget was $9.4 million.

Dr. SHANNON. There is one figure that makes it difficult to compute this. We can get figures from industry, that supports roughly 25 percent of all medical research in this country, but it is impossible to get the breakdown. You have roughly one-fourth industrial activity.

Mr. MICHEL. Of course with all the Federal Government is doing we leave very little real incentive to the private sector to do anything extravagant on their own.

Dr. FREDRICKSON. There are a large number of foundations that make contributions to heart research that are very important. The Hartford Foundation, the John Hay Whitney Foundation, and the Life Insurance Medical Research Fund are three that make significant contributions. There are many others.

ACUTE CORONARY CARE UNITS

Mr. MICHEL. You go from six to 12 acute coronary care units for research.

Dr. FREDRICKSON. This program has just been activated this year and funds for approximately six of the 12 centers will be obligated in the last 2 months of the year. At the present time we have 43 proposals for 43 institutions competing for what probably will be five or six such contract awards this year. They are undergoing primary review now and will undergo a secondary review in May.

Mr. MICHEL. Could we have a list of the 43 that have been received up to this point?

Dr. FREDRICKSON. Yes, I will be very glad to supply that.

(The information follows:)

INSTITUTIONS RESPONDING TO FIRST ANNOUNCEMENT OF NATIONAL HEART INSTITUTE MYOCARDIAL INFARCTION STUDY CENTERS

The University of Alabama Medical Center, 1919 7th Avenue, South, Birmingham, Ala.
Albert Einstein College of Medicine, Yeshiva University, Eastchester Road & Morris Park Avenue, Bronx, N.Y.
Albert Einstein Medical Center, York and Tabor Roads, Philadelphia, Pa.
Cedars-Sinai Medical Center, 4833 Fountain Avenue, Los Angeles, Calif.
The University of Chicago, 950 East 59th Street, Chicago, Ill.
University of Cincinnati, Cincinnati 29, Ohio.
City of Hope Medical Center, 1500 E. Duarte Road, Duarte, Calif.

Cox Coronary Heart Institute, 3525 Southern Boulevard, Kettering, Ohio.
Duke University Medical Center, Durham, N.C.
General Rose Memorial Hospital, 1050 Clermont Street, Denver, Colo.
Georgetown University Hospital, 3800 Reservoir Road NW., Washington, D.C.
The George Washington University Hospital, 901 23d Street NW., Washington, D.C.
Gerontology Research Institute, The Sansum Clinic Research Foundation, 317 West Pueblo Street, Santa Barbara, Calif.
Harvard Medical School, Massachusetts General Hospital, Boston, Mass.
Indiana University Medical Center, 1100 West Michigan Street, Indianapolis, Ind.
The Johns Hopkins Hospital, 725 North Wolfe Street, Baltimore, Md.
The Long Island College Hospital, 340 Henry Street, Brooklyn, N.Y.
Lovelace Clinic and Lovelace Foundation, 5200 Gibson Boulevard, S.E., Albuquerque, N. Mex.
Marshfield Clinic Foundation, 630 S. Central Avenue, Marshfield, Wis.
The Mason Clinic, 1118 Ninth Avenue, Seattle, Wash.
Mayo Clinic, 200 First Street Southwest, Rochester, Minn.
The University of Mississippi Medical Center, 2500 North State Street, Jackson, Miss.
Mount Sinai Hospital of Greater Miami, 4300 Alton Road, Miami Beach, Fla.
The Mount Sinai Hospital, 100th Street and Fifth Avenue, New York, N.Y.
The New York Hospital, Cornell Medical Center, 525 East 68th Street, New York, N.Y.
State University of New York, 450 Clarkson Avenue, Brooklyn, N.Y.
The Ohio State University, 410 West 10th Avenue, Columbus, Ohio.
University of Oklahoma, Medical School, Oklahoma City, Okla.
University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, Oreg.
Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Mass.
The Institute of Medical Sciences, Presbyterian Medical Center, Clay and Webster Streets, San Francisco, Calif.
Presbyterian—University of Pennsylvania Medical Center, Fifty One North 39th Street, Philadelphia, Pa.
University of Southern California, Los Angeles County Hospital, Los Angeles, Calif.
St. Joseph's Research Laboratory, 69 West Exchange Street, St. Paul, Minn.
St. Vincent's Hospital and Medical Center, 153 West 11th Street, New York, N.Y.
University of Texas, Southwestern Medical School and Parkland Memorial Hospital, Dallas, Tex.
The University of Utah Medical Center, Salt Lake City, Utah.
U.S. Public Health Service Hospital, Staten Island, N.Y.
Medical College of Virginia, 1200 East Broad Street, Richmond, Va.
Washington University, Barnes and Wohl Hospitals, 660 South Euclid Avenue, St. Louis, Mo.
University of Washington, 211 Administration Building, Seattle, Wash.
Wayne State University, 1400 Chrysler Freeway, Detroit, Mich.
The Wesley Medical Center, 550 North Hillside, Wichita, Kans.

UNDERGRADUATE TRAINING GRANTS IN ILLINOIS

Mr. MICHEL. Could you place in the record the undergraduate schools in Illinois that have received training grants, if any?

Dr. FREDRICKSON. Yes, sir.

Dr. SHANNON. You mean medical schools?

Mr. MICHEL. Would they be confined to medical schools?

Dr. FREDRICKSON. The undergraduate grants could be awarded to medical schools, schools of osteopathy, or schools of public health. There are six such. We will put them in the record.

(The information follows:)

National Heart Institute Undergraduate Training Grants in Illinois

Program Director	*Institution*
1. Hans H. Hecht	University of Chicago.
2. Granville A. Bennett	University of Illinois College of Medicine.
3. Peter J. Talso	Loyala University, Stritch School of Medicine.
4. Aldo A. Luisada	Chicago Medical School.
5. Oglesby Paul	Northwestern University.
6. George T. Caleel	Chicago College of Osteopathy.

Mr. MICHEL. Is there a distinction between the grants to graduate students?

Dr. SHANNON. Undergraduate in one context means prebaccalaureate but in ours it means pre-M.D.

Mr. MICHEL. That is all.

Mr. FLOOD. Mr. Smith.

COORDINATION WITH RESEARCH UNDER NON-GOVERNMENT FUNDS

Mr. SMITH. Does your advisory committee, at the time they meet to determine who shall receive contracts and grants, have available to it information concerning what work is going to be done by non-Government funds?

Dr. FREDRICKSON. Yes, sir. The special contract review committees have the specific contract proposals which they examine in detail.

Mr. SMITH. You just indicated about 20 percent of the research funds are raised and spent by non-Government sources. Prior to formulating your program, do you know what these non-Government sources are going to be doing so there will not be duplication?

Dr. FREDRICKSON. They usually know from their own knowledge because they are specialists in the area involved.

Mr. SMITH. You think you are able to avoid unnecessary duplication?

Dr. FREDRICKSON. I think we are, sir.

CPIB

Mr. SMITH. On page 3 of your special report of November the report states with regard to CPIB:

"Clinical experience with the drug has been too limited to determine whether it will retain its effectiveness and freedom from side effects after long use."

I notice the FDA recently cleared this drug. Are you in disagreement with the FDA?

Dr. FREDRICKSON. We are not in disagreement with the FDA. This drug was released, I believe, last month. The drug CPIB has been used in about an estimated—and it is a very rough estimate—20,000 people in this country and abroad. Perhaps more in the United Kingdom than America at the present time. These individuals have received the drug for varying periods of time up to 2 years or more; there has not yet been a single major side effect from this drug reported.

Mr. SMITH. So although you do not know for sure, you think the advantages are worth more than the possibility that there would be side effects?

Dr. FREDRICKSON. Yes. It is a very effective drug in lowering certain of the blood fats.

Mr. SMITH. The risk of side effects is a risk you ought to take to get the benefits of the drug.

Dr. FREDRICKSON. This risk would seem to be quite small, although never negligible, sir.

PARGYLINE

Mr. SMITH. On page 6 of this report, and referring to pargyline, it says, "Some earlier MAO inhibitors tested proved so toxic that the future MAO inhibitors as an approach to hypertension therapy look bleak indeed." Then it says that pargyline is a new breed. But the manufacturer has been required to send the same warning letters on this new drug that they did on the other.

Is this inconsistent with your findings or not?

Dr. FREDRICKSON. I do not believe it is, sir. The drug has certain effects in common with the other older hydrazine derivatives which also had the same enzyme blocking effect.

Mr. SMITH. I am speaking of the warning letters against eating cheese and certain kinds of food.

Dr. FREDRICKSON. Yes, because cheese contains certain materials whose normal metabolism is blocked in the presence of this drug——

Mr. SMITH. There are still common elements.

Dr. FREDRICKSON. Yes, sir.

HEART ASSIST DEVICES

Mr. SMITH. Within the past year I noticed on at least two different occasions that NIH grantees have made news headlines by inserting heart assist devices into patients, which raises the question as to whether these different grantees were duplicating one another's efforts.

Dr. FREDRICKSON. No, they were not. Each has developed and is testing a different kind of pump to assist the left ventricle. They are significantly different from each other.

Mr. SMITH. Were they aware at all times as to what each one was doing?

Dr. FREDRICKSON. Yes, I am certain they were. The differences between these devices are important.

Mr. NATCHER. Mr. Hull.

Mr. HULL. No questions.

Mr. NATCHER. Mr. Casey?

DIET HEART FEASIBILITY STUDY

Mr. CASEY. I am interested in the diet heart feasibility study.

You say it has been completed and will be available to the Institute before the middle of 1967. What has happened between now and the middle of 1967?

Dr. FREDRICKSON. They have their last results in, but the biometricians are now analyzing the results. The members of the committee

are actually now writing that report. So between the final analyses of the results and the preparation of the report they are actually firming up their conclusions.

Mr. CASEY. They have completed all the study aspects but have not completed the report?

Dr. FREDRICKSON. They have not completed the analysis of their data but they have practically done so.

CHOLESTEROL

Mr. CASEY. Have they ever settled the argument on cholesterol?

Dr. FREDRICKSON. Not entirely, sir. Certainly not to everyone's satisfaction.

Mr. CASEY. You can walk down the street, theoretically, and every other doctor will have a different opinion.

Dr. FREDRICKSON. Yes.

Mr. CASEY. They won't be in accord. Do you think this report might have some bearing on settling that argument?

Dr. FREDRICKSON. I think this report will have a bearing on settling that argument only in that it will tell us whether it might be feasible to take another major step toward settling it, if I make myself clear. The question of whether you can alter the American diet for a limited period is what this study attempted to answer. If it says you can then we must make a decision whether we should so alter the diet in enough Americans to tell us whether this alteration makes a difference in coronary heart disease.

Mr. CASEY. I know if you take somebody that is fairly thin and they put them on a cholesterol-free diet, sometimes the so-called cure is worse than the threat, because they get pretty weak and lose a lot of weight they cannot afford to lose, when you start taking everything out of their diet that has any fat in it whatsoever.

Dr. FREDERICKSON. We think that one must be very cautious in making recommendation to any single individual and certainly to large groups of people about any content of the diet. Cholesterol in the diet or in the blood is not the only factor related to the development of atherosclerosis. I am certain it is a factor, however.

RATE OF GROWTH FOR HEART RESEARCH

Mr. CASEY. Do you feel we are maintaining a proper rate on all your research that you think should be conducted at this time in your heart program; not only your mechanical but your other aspects of your heart program?

Dr. FREDRICKSON. Sir, do you mean is the rate of achievement——

Mr. CASEY. Are you moving at a satisfactory rate?

Dr. FREDRICKSON. I think we are.

Mr. CASEY. With what you can handle? I know lots of people do not think you are moving fast enough. As the chairman said, we would like to have a cure at 4 o'clock this afternoon but you are not going to accomplish that. Do you think the level of the endeavor is something that you are proud of and that you feel you can continue to show gains?

Dr. FREDRICKSON. I think within the resources we have we are using them well and we are making achievements, sir.

Mr. CASEY. On your engineering aspects, are those selected by you or are they selected by the prime recipient of the grant in your programs?

Dr. FREDERICKSON. The questions that these contracts serve to answer are selected by our program office and by our advisers. The exact means by which the contractor may seek to answer the questions posed may be selected by him. But we have to approve his approach.

Mr. CASEY. Is engineering getting more in the medical field all the time?

Dr. FREDRICKSON. Yes.

Mr. CASEY. I do not mean the structural engineers, but all phases, the electrical engineer primarily, I imagine, as well as the fine mechanical engineers, as I call them.

Dr. FREDRICKSON. Yes. The relationship between engineers and biologists is now important and will become increasingly so in the future.

Dr. SHANNON. There is a very interesting development that you might be interested in. In your own city of Houston, there is a relationship between Baylor and Rice and the Methodist Hospital. In the city of Cleveland, Western Reserve University has now joined in a common enterprise with Case Technological Institute. In Boston, there is developing a program, which we will look at later in the year, that will represent a combined effort between MIT and the Harvard Medical School. So not only are engineers in general becoming more heavily engaged in the biological and medical problems—and I might say this is particularly true in the aerospace industry—but the academic environments are finding a need for a much more intimate relationship than obtained in the past. This bodes very well because what we need are the type of hybrid scientists who know the physical sciences and engineering, on the one hand, and the biological and medical problems on the other. On the development of such hybrid scientists depends the real application of the engineering talents of the nation to serious medical problems. This cannot be done without this type of associated relationship. This is developing very rapidly.

Mr. CASEY. Doctor, you just put in better words what I wanted to put in the record, the fact that Rice and Baylor and the Methodist Hospital have gone into this very deeply and are getting more interested in it, and Rice particularly sees the need for the training of more specialized engineers in this field. I think it is something that probably we will see more of, as you noted there, throughout the country. I have no more questions.

Mr. FLOOD. I may say for your baptism of fire you came through with flying colors.

Dr. FREDRICKSON. Thank, you sir.

JUSTIFICATION MATERIAL

National Heart Institute

Amounts available for obligation

	1967	1968
Appropriation	$164,770,000	$167,954,000
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (space rental)	−13,000	0
Comparative transfers within NIH	−781,000	0
Total	163,976,000	167,954,000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$105,996,000		$106,628,000		+$632,000
General research support grants		(8,943,000)		(10,108,000)		(+1,165,000)
Scientific evaluation and planning		(163,000)		(163,000)		0
Categorical clinical research centers		(4,500,000)		(4,500,000)		0
Heart cooperative drug study		(3,820,000)		(3,820,000)		0
Specialized research centers		(800,000)		(800,000)		0
Fellowships		6,975,000		7,439,000		+464,000
Training		17,525,000		17,696,000		+171,000
Direct operations:						
Laboratory and clinical research	402	11,469,000	411	13,135,000	+9	+1,666,000
Collaborative research and development	51	16,428,000	51	17,526,000	0	+1,098,000
Biometry, epidemiology, and field studies	87	1,590,000	87	1,727,000	0	+137,000
Training activities	17	289,000	17	295,000	0	+6,000
Review and approval of grants	105	2,571,000	105	2,663,000	0	+92,000
Program direction	33	818,000	33	845,000	0	+27,000
Total obligations	695	163,661,000	704	167,954,000	+9	+4,293,000
Unobligated balance, reserve	0	315,000	0	0	0	−315,000
Total obligations and balance	695	163,976,000	704	167,954,000	+9	+3,978,000

Obligations by objects

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	695	704	+9
Full-time equivalent of other positions	55	55	0
Average number of all employees	687	696	+9
11 Personnel compensation:			
Permanent positions	$5,768,000	$5,846,000	+$78,000
Positions other than permanent	229,000	229,000	0
Other personnel compensation	79,000	79,000	0
Total personnel compensation	6,076,000	6,154,000	+78,000
12 Personnel benefits	658,000	662,000	+4,000
21 Travel and transportation of persons	275,000	294,000	+19,000
22 Transportation of things	98,000	98,000	0
23 Rent, communications, and utilities	177,000	190,000	+13,000
24 Printing and reproduction	35,000	35,000	0
25 Other services	1,424,000	1,679,000	+255,000
Project contracts	16,064,000	17,121,000	+1,057,000
Payment to "National Institutes of Health management fund"	6,555,000	7,430,000	+875,000
26 Supplies and materials	1,101,000	1,590,000	+489,000
31 Equipment	722,000	958,000	+236,000
41 Grants, subsidies, and contributions	130,496,000	131,763,000	+1,267,000
Subtotal	163,681,000	167,974,000	+4,293,000
Deduct quarters and subsistence charges	−20,000	−20,000	0
Total obligations by object	163,661,000	167,954,000	+4,293,000

Summary of changes

1967 enacted appropriation	$164,770,000
Transferred to "Operating expenses, Public Building Service," General Services Administration (space rental)	−13,000
Comparative transfers within NIH	−781,000
Unobligated balance, reserve	−315,000
1967 total estimated obligations	163,661,000
1968 estimated obligations	167,954,000
Total change	+4,293,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in:				
1. Annualization of wage board pay increase in 1967				$2,000
2. Annualization of new positions authorized in 1967				12,000
B. Program:				
1. Research grants		$105,996,000		632,000
2. Fellowships		6,975,000		464,000
3. Training grants		17,525,000		171,000
4. Laboratory and clinical research	402	6,727,000	9	872,000
5. Collaborative research and development	51	16,359,000		1,093,000
6. Biometry, epidemiology, and field studies	87	1,472,000		131,000
7. Direct training	17	266,000		4,000
8. Review and approval of grants	105	1,193,000		48,000
9. Program direction	33	583,000		6,000
Total program increases			9	3,421,000
Payment to National Institutes of Health management fund for centrally furnished services:				
Laboratory and clinical research		794,000		
Collaborative research and developments		5,000		
Biometry, epidemiology, and field studies		9,000		
Direct training		2,000		
Review and approval of grants		45,000		
Program direction		20,000		
Total				875,000
Gross increases				4,310,000
DECREASES				
1 less day of pay (261 days in 1967; 260 days in 1968)				−17,000
Total net change requested				+4,293,000

EXPLANATION OF CHANGES

Research grants.—The net increase of $632,000 will provide $4,781,000 for the competing continuation of existing regular program project grants and $1,165,000 for general research support grants. These increases are partially offset by a decrease of $5,314,000 in noncompeting continuation awards.

Fellowships.—The increase of $464,000 will provide $1,034,000 for the noncompeting continuation of current awards, partially offset by a decrease of $570,000 in new and competing awards. It will provide an increase of 33 awards over the 1967 level for the research career development award program.

Training grants.—The increase of $171,000 will provide for additional indirect costs in the undergraduate cardiovascular training area.

Laboratory and clinical research.—The program increase of $872,000 and 9 positions will provide: $32,000 and 2 positions for a blood donor program for dogs; $380,000 for increased dog procurement costs; $460,000 and 7 positions to outfit and utilize newly assigned space for expansion of present programs.

Collaborative research and development.—The program increase of $1,093,000 will be used to further research and development of the National Blood Resource Program.

Biometry, epidemiology and field studies.—The program increase of $131,000 will provide for grant-related contracts (example, vasoactive peptides).

Direct training.—The program increase of $4,000 will provide for additional tuition costs.

Review and approval of grants.—The program increase of $48,000 will provide for consultant services.

Program direction.—The program increase of $6,000 will provide for consultant services.

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."

The Public Health Service Act, Title IV, National Research Institutes, Part B National Heart Institute—

"Sec. 411. There is hereby established in the Public Health Service a National Heart Institute (hereafter in this part referred to as the "Institute").

"Sec. 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 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

	1967 estimate	Purpose
Transferred to "Operating expenses, Public Buildings Service," General Services Administration.	−$13,000	Transfer of rental costs to General Services Administration.
Comparative transfer within NIH	−781,000	To provide for the revised formula distribution of the NIH management fund.

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$87,770,000	$87,237,000	−$533,000
Special programs	18,226,000	19,391,000	+1,165,000
Total research grants	105,996,000	106,628,000	+632,000

REGULAR PROJECTS

Introduction

In its search for the cure, alleviation, and prevention of cardiovascular diseases, the National Heart Institute will support approximately 2,000 research projects through research grants in 1967 and 1968. Most of these projects are a continuation of ongoing research; in their great scope and diversity they range from epidemiological studies on large population groups down through 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 protein 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 susceptibility to the disease may be influenced by such factors as age, sex, diet, physical activity, psychic stress, and other factors. Congenital heart disease may arise from genetic factors or from a variety of noxious pre-natal factors affecting the fetus at critical stages of its development. For such reasons it has been both necessary and desirable to deploy our research manpower and resources along a wide variety of research approaches.

The following list identifies the major cardiovascular-disease research areas. *Atherosclerosis*, the presence in arteries of fatty plaques that interfere with blood flow, is the most prevalent of all cardiovascular disorders, causing nearly one million deaths per year in America. Complications from this disease include heart attacks, strokes, and congestive heart failure. There has been nearly a ten-fold increase in the number of research projects in this field in the past decade; and currently, in terms of research funds expended for regular grant programs, atherosclerosis is the largest single disease category in the Heart Institute program.

Hypertension—high blood pressure—is one of the most commonly encountered forms of cardiovascular disease. It is estimated that seventeen million Americans between the ages of 18 and 79 have definite hypertension, with 10.5 million adults suffering from hypertensive heart disease, one of the consequences of hypertension. Hypertension aggravates and accelerates the development of atherosclerosis and is a major cause of strokes, heart failure, and kideny failure.

Cerebrovascular diseases—strokes—account for the third largest cause of death annually in the United States—a toll exceeded only by heart disease and cancer. While the most common cause of stroke is blood clots forming in the arteries supplying the brain, strokes are not a discrete medical entity. They are inherently related to other circulatory diseases. Hypertension predisposes patients to strokes; atherosclerosis may weaken blood vessels supplying the brain, predisposing them to rupture, and atherosclerosis deposits in such vessels create conditions favorable to the formation of blood clots.

Congenital heart disease is the main cause of death in infants under two years of age and is one of the costliest of all diseases in its medical care. Knowledge of the causes, development and natural history of congenital heart disease is far from adequate.

Rheumatic fever and heart disease continues to occur in significant numbers even though the full application of existing knowledge and techniques could prevent a large proportion of initial and recurrent attacks. Continued prevalence of this disease is due to several deficiencies: existing methods of disease control fall short of the ideal, gaps remain in current methods of prevention, and existing knowledge is not applied.

During the last two decades there has been increasing recognition that the heart and lungs are not two systems, but one—the cardiopulmonary system. The incidence of *cardiopulmonary diseases*, particularly emphysema, is increasing. Not less than 10% of middle-aged and elderly Americans are afflicted with emphysema. As a disenabling disease, it is second only to heart disease; disability allowances now exceed eighty million dollars each year.

The problem of *congestive heart failure and shock* is a large and diffuse one. These are not discrete diseases, but rather symptom-complexes that are often the end results of underlying cardiovascular diseases.

Death and disability from *coronary artery disease* represents the greatest single challenge to modern medicine. The mechanisms by which coronary atherosclero-

sis causes death and disability involve a broad range of biologic phenomena and of medical manifestations. These range from life-threatening events such as myocardial infarction and cardiac arrhythmias, to major disability from angina pectoris, and must also include psychological problems. All of these may interrelate in complex ways with normal and abnormal function of other body systems.

Maintenance of the normal state of the blood bears an essential relationship to the health of the heart and blood vessels. *Thrombosis* or clotting of the blood within vessels is one of the principal immediate causes of death. Conversely, failure of the blood to clot properly is responsible for much morbidity and mortality from a variety of bleeding diseases and from hemorrhage at surgey. Furthermore, blood factors are indispensible in the management of diseases including anemia, leukemia, infectious diseases, hemorrhage and thrombotic diseases and traumatic shock.

Summaries of some of the results of research support in 1966 pertaining to these research areas appear in the research highlights that accompany the statement of the Director, National Heart Institute.

Program plans in 1967 and 1968

Plans for these two years are primarily a continuation of current research areas as indicated in the following research grants program analysis table.

A decrease of $5,314,000 in noncompeting continuations is offset by a corresponding increase in competing projects. This change is needed to continue support of 14 program projects whose long term noncompeting commitment (7 years) expires with their 1967 award and which have been approved as competing renewal awards for 1968.

Special Programs

The only request for increased support in 1968 is for $1,165,000 for *General Research Support Grants*. This increase represents the Institute's proportionate share of the proposed National Institutes of Health increase in this area.

The same level of support, $4,500,000 is continued from 1967 to 1968 in *Categorical Clinical Research Centers* for the research resources of in depth, multidisciplinary investigations in the cardiovascular area.

Undoubtedly, atherosclerosis and its complications represent this country's foremost health challenge. In the desire to reduce heart attacks and strokes, the major (and more difficult) objective is reducing atherosclerosis. In this problem there is a scientific consensus, based upon a host of well validated studies, that atherosclerosis may be prevented or its advance in the population greatly decelerated; it may be partially reversible. *The Heart Cooperative Drug Study* is a planned, directed effort toward these ends.

The Heart Institute is undertaking to establish and support a limited number of highly selected *Specialized Cardiovascular Research Centers* of excellence in which large and stable investments are deliberately made in groups of investigators capable of imaginative and creative research of which clinical investigation will be an important element. This coordinated approach was developed when it became evident that only by the combined efforts of specialists in various basic and clinical disciplines could causes be uncovered and cures achieved for such complex and pervasive disorders as the cardiovascular diseases. Moreover, within each discipline, the complexity of methodology and technology have created subdisciplines requiring discrete skills and knowledge. To bring together representatives of these numerous specialties to focus on a common problem requires an environment where they can interact and profit from each other's knowledge and experience. Equally important are the training opportunities to be provided in such a setting for the development of young scientists who can think beyond their own specialties and who can grow with the rapidly changing modern scientific scene.

Viewed in an even larger context, advances in such disparage fields as materials research, electrical engineering, chemistry, and analytical methodology often contribute to the solution of cardiovascular disease problems. However, if the benefits from these advances are to be made available to the patient with heart disease, a research environment must be provided in which scientists from these varied fields can find professional satisfaction in what would otherwise be regarded as a purely clinical setting. This consideration imposes the requirement that the research setting acquire a certain "critical mass" in order for it to be maximally effective as an interdisciplinary activity.

Finally, if research results are to be applied to improve patient care in the shortest possible time, the biomedical research environment must include

clinicians concerned with problems of patient care. The symbiotic collaboration between clinician and researcher represents the final step in the development of new treatments of heart diseases.

The National Heart Institute proposes to provide support for interdisciplinary research programs mainly through two support devices: the program project grant (for which Categorical Clinical Center funds provide resource support) and the Specialized Cardiovascular Research Center grant. Both of these grant mechanisms are designed to encourage the team approach. However, they differ in that program projects are concerned *in depth* with a specific aspect of heart disease, whereas cardiovascular research centers will be equipped to implement clinical and basic research and training programs of considerable depth and *breadth*.

During 1966 the National Heart Institute awarded four planning grants for the future development of Specialized Cardiovascular Research Centers. It is expected that the planning phase will continue through 1967 and 1968 at a level of $800,000.

Research grants program analysis

	1967 estimate	1968 estimate	Increase or decrease
Atherosclerosis	$16,852,000	$16,750,000	−$102,000
Hypertension	13,078,000	12,998,000	−80,000
Cerebrovascular diseases	1,931,000	1,919,000	−12,000
Congenital heart disease	6,846,000	6,804,000	−42,000
Rheumatic fever and heart disease	2,896,000	2,879,000	−17,000
Cardiopulmonary diseases	6,144,000	6,107,000	−37,000
Heart failure and shock	15,974,000	15,877,000	−97,000
Coronary artery disease	6,934,000	6,892,000	−42,000
Thromboembolic and hemorrhagic diseases	8,601,000	8,549,000	−52,000
Other cardiovascular diseases	8,514,000	8,462,000	−52,000
Subtotal	87,770,000	87,237,000	−533,000
General research support grants	8,943,000	10,108,000	+1,165,000
Scientific evaluation	163,000	163,000	0
Categorical clinical research centers	4,500,000	4,500,000	0
Heart cooperative drug study	3,820,000	3,820,000	0
Specialized research centers	800,000	800,000	0
Total research grants	105,996,000	106,628,000	+632,000

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Noncompeting continuations	1,514	$63,456,000	1,318	$58,142,000	−196	−$5,314,000
Competing continuations	300	10,000,000	274	15,314,000	−26	+5,314,000
New projects	267	9,314,000	228	8,781,000	−39	−533,000
Supplementals	(350)	5,000,000	(325)	5,000,000	(−25)	0
Subtotal regular program	2,081	87,770,000	1,820	87,237,000	−261	−533,000
General research support grants		8,943,000		10,108,000		+1,165,000
Scientific evaluation and planning		163,000		163,000		0
Categorical clinical research centers		4,500,000		4,500,000		0
Heart cooperative drug study		3,820,000		3,820,000		0
Specialized research centers		800,000		800,000		0
Total research grants		105,996,000		106,628,000		+632,000

Fellowships

	1967 estimate	1968 estimate	Increase or decrease
Total fellowships	$6,975,000	$7,439,000	+$464,000

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 1967 and 1968

In the postdoctoral and special programs 312 awards are expected to be supported in both 1967 and 1968. 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. Through the special research fellowship award the more advanced scientists is exposed to improved methods and is able to attain new skills by means of unusual training experience in research laboratories other than his own.

The research career development award program supports the younger investigator of demonstrated ability. The increase of $414,000 and 33 awards in 1968 will allow for a continued expansion of this most productive program, which is helping to insure the supply of biomedical research scientists adequately trained to guarantee the quality of health research in the future. The research career award program will continue to provide stable support for the senior investigator.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Continuations:						
Noncompeting	229	$3,689,000	309	$4,723,000	+80	+$1,034,000
Competing	92	1,225,000	67	882,000	−25	−343,000
Supplementals	(23)	30,000	(23)	30,000	0	0
New	201	2,031,000	179	1,804,000	−22	−227,000
Total fellowships	522	6,975,000	555	7,439,000	+33	+464,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Postdoctoral	225	$1,600,000	225	$1,600,000	0	0
Special	87	725,000	87	725,000	0	0
Research career:						
Career	38	1,050,000	38	1,100,000	0	+$50,000
Development awards	172	3,600,000	205	4,014,000	+33	+414,000
Total fellowships	522	6,975,000	555	7,439,000	+33	+464,000

Training Grants

	1967 estimate	1968 estimate	Increase or decrease
Total training grants	$17,525,000	$17,696,000	+$171,000

INTRODUCTION

The National Heart Institute through its training grant programs aims at (1) upgrading the quality of research training, which provides concepts and techniques in cardiovascular research, and (2) attracting promising young students to careers in medical research to insure a continuing and expanding supply of cardiovascular scientists and teachers adequately trained to guarantee the quality of health research in the future. Undergraduate training grants are awarded to medical schools to establish, expand, improve, or continue instruction relating to prevention, diagnosis, and treatment of cardiovascular disease. In the graduate area, the ideal training program combines teaching and research to stimulate and train in the potential productive investigator.

Program plans in 1967 and 1968

Undergraduate Training Grants

There are 108 undergraduate schools receiving support in 1967 and all have a continuing commitment in 1968. The 108 schools, located in 40 states, the District of Columbia, and Puerto Rico include 90 four-year schools at $25,000 per school and 18 two-year schools at about $15,000 per school. The net program increase of $171,000 will provide for additional indirect costs.

Graduate Training Grants

Graduate training grants support advanced training programs in basic and clinical cardiovascular research in medical schools, universities, or other research-educational organizations. This instrument permits local identification of young men and women with research potential, provides them with appropriate stipends, and assists the institution to improve the quality of research training. This type of grant is an effective means of bringing basic and clinical scientists together in broader study of cardiovascular diseases through training involving multiple disciplines and several departments.

In recognition of the great need for a large corps of high quality practicing clinicians equipped with the necessary training in diagnosis and treatment of cardiovascular problems, the National Heart Institute in 1966 awarded 18 graduate clinical training grants. It is expected that the National Advisory Heart Council will recommend for approval 18 additional applications in 1967. These will be the physicians who will have the greatest impact in transferring the fruits of research to the care of patients.

The Institute will meanwhile continue its graduate research training program where a majority of trainees will continue to receive multidisciplinary cardiovascular training, with emphasis being placed on physiology, surgery, and internal medicine.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Continuations:						
Noncompeting	329	$14,304,000	357	$16,623,000	+28	+$2,319,000
Competing	50	2,711,000	15	810,000	−35	−1,901,000
Supplementals	(7)	117,000	(7)	117,000	(0)	0
New	12	393,000	4	146,000	−8	−247,000
Total, training grants	391	17,525,000	376	17,696,000	−15	+171,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Undergraduate	108	$2,427,000	108	$2,670,000	0	+$243,000
Graduate	283	15,098,000	268	15,026,000	−15	−72,000
Total, training grants	391	17,525,000	376	17,696,000	−15	+171,000

LABORATORY AND CLINICAL RESEARCH

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefit	402	$4,238,000	411	$4,323,000	+9	+$85,000
Other expenses	-------	7,231,000	-------	8,812,000	-------	+1,581,000
Total	402	11,469,000	411	13,135,000	+9	+1,666,000

INTRODUCTION

Laboratory and clinical research programs have their major emphasis upon basic physiological and biochemical studies of the cardiovascular system which seek new knowledge about its structure, function, and abnormalities. The need for a broad program of basic research is founded on the knowledge that the cardiovascular diseases appear to have their roots in the subtle and complex processes of body metabolism and in the mechanisms by which these processes are controlled. Therefore such basic studies are essential to understanding the underlying causes of these diseases, and on the basis of such knowledge, seeking means of preventing or curing them. Closely associated with the basic studies are clinical studies concerned with the application of fundamental knowledge to the diagnosis, prevention, and treatment of diseases of the heart and blood vessels.

Program plans in 1967 and 1968

In 1967 the Laboratory of Cardiovascular Diseases has been phased out and two former laboratory sections are being elevated to full laboratory status: the Laboratory of Biochemical Genetics and the Laboratory of Molecular Diseases. In 1968 the program will generally be a continuation of present programs with further shifts of emphasis where new knowledge or necessity dictates.

The program increase of $872,000 and 9 positions needed for effective research for the coming year will be used as follows:

(1) Two positions and $32,000 to initiate a program which will establish a colony of dogs to be used as bleeders from which blood may be drawn for transfusion to dogs used in surgical experiments. Heretofore most dogs used in such experiments would have to be sacrificed; the infusion of canine blood will allow recovery and reuse of many of these animals. The object of this program is to decrease the number of research dogs used which will result in a significant savings in their acquisition cost. This is particularly important in view of the drastic cost increase anticipated in the procurement of research animals.

(2) $380,000 to assure the provision of adequate numbers of dogs for research. There is every evidence that the cost of procuring research animals—particularly dogs—will escalate drastically by 1968 owing to Congressional legislation which requires that sellers of dogs be licensed and subject to inspection. Increased costs associated with improving the dog breeding environment are expected to be passed on to the consumers. The Heart Institute used 4,532 research dogs in 1966 at a cost of $121,000 or an average cost of about $27 per dog. It is estimated that the cost of each dog in 1968 will average $120. Because of the dog blood donor program described above, it is estimated that the Heart Institute will decrease its dog usage to approximately 4,200 by 1968. The $500,000 required for dog procurement in 1968 is partially offset by the $120,000 available in the current 1967 budget.

(3) Seven positions and $460,000 to outfit and utilize newly assigned space for expansion of present programs. In 1968 laboratory and clinical research will be assigned additional space equivalent to half a laboratory wing in the NIH Clinical Center. The new modules will be assigned to the Laboratory of Metabolism, Laboratory of Clinical Biochemistry, Experimental Therapeutics Branch, and the newly created Laboratory of Biochemical Genetics to permit studies which have not been possible because of limited space. Overflow of present staff into the new quarters will reduce the number of positions which would normally be needed for expansion into a laboratory wing.

Included in the increase is $10,000 for mandatory items such as annualization of positions new in 1967 and annualization of wage board pay increase in 1967, offset by $10,000 for one less day of pay in 1968. There are also increases of $794,000 for centrally furnished services from the "National Institutes of Health Management Fund".

COLLABORATIVE RESEARCH AND DEVELOPMENT

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	51	$176,000	51	$176,000	0	0
Other expenses		16,252,000		17,350,000		+$1,098,000
Total		16,428,000		17,526,000		+1,098,000

INTRODUCTION

This activity is responsible for administering (1) the *Artificial Heart-Myocardial Infarction Program*, (2) the direct support of the *Heart Cooperative Drug Study*, and (3) the *National Blood Resource Program*.

Program plans in 1967 and 1968

Artificial Heart-Myocardial Infarction

Myocardial infarction, a principal form of heart attack, is the largest cause of death in the Nation today. Every year about 750,000 Americans suffer such attacks and, by conservative estimates, more than 350,000 are killed by them. The Artificial Heart-Myocardial Infarction Program is an organized research effort designed to improve understanding and treatment of myocardial infarction and the myocardial insufficiency which results from this and other diseases. The program includes substantial elements of goal-oriented biomedical research covering a broad spectrum of pertinent fields as well as a major bioengineering effort leading to the development of mechanical circulatory assist devices which can be used to support the failing heart. Both parts of the program offer real and early prospect of providing the means for improved treatment of myocardial infarction with consequent lowering of mortality and increased human salvage.

The immediate aims of the Bioengineering Branch are the most rapid, efficient, and inexpensive development of temporary circulatory assist devices and definition of the predictability of patients in whom they may be of value. Longer range goal is the acquisition of data and experience permitting development of a permanently implanted artificial heart should continuing analysis indicate this to be a feasible and desirable goal. The program is applying rigorous methods of systems analysis and systems development. Program definition has been provided in part by a group of parallel study contracts which analyzed the need for circulatory assist devices, and the state of the art in various pertinent technological areas, the specific problems needing more research, and the feasibility of the program. In addition, these studies provided plans for direction, magnitude, and timing of a development program, and documented the need for technological advancement in several major areas as a prerequisite for successful development of circulatory assist devices. A contracts program is planned which will reach an operating level of about 50 contracts per year. The following specific problems need urgent resolution: the development of a long-term percutaneous lead system, for ultimate use in ambulatory humans, to transmit electrical or fluid energy into the thoracic cavity for energizing circulatory assist devices; the development of practical automatic control mechanisms for assist devices; the development of basic theorems and fundamental data pertaining to blood flow at such sites as prosthetic valves, points of connection, and pumping areas in order to define the design limits of devices; the development of a material that is compatible with blood and possesses the physical characteristics required for assist devices; the development of energy sources and conversion and transmission systems for ultimate implantation; and the establishment of tolerances and limits of vibration, radiation, weight, etc., as they relate to device development. Throughout the development of assist devices, appropriate testing and evaluation in animals, and later in man, will take place.

The Medical Branch is responsible for developing a research program designed to improve the prospects of survival following myocardial infarction by the support of research which has the purpose of improving understanding, diagnosis, and treatment of myocardial infarction. An important part of this responsibility is the early development of medical criteria for the use and evaluation of circulatory assist devices and the provision of biomedical support for the developmental efforts of the Bioengineering Branch.

The medical program is now in the stage of program definition. At this time, it appears that the systems analysis and development methods as used by the Bioengineering Branch will not be appropriate to the task of the Medical Branch and other means of program organization and design will need to be used. Major elements of initial program content are now clearly established and will include: (1) From 6 to 12 clinical myocardial infarction study centers equipped and staffed to provide optimal patient care while making critical research observations during acute myocardial infarction. These will require highly sophisticated instrumentation and coordinated collection of information. There have been very few systematic and thorough studies of patients with acute myocardial infarction and there are consequent major uncertainties concerning the cause, the deter-

minants of survival, the specific cause of death and the effects of treatment. These uncertainties must be resolved to allow rational development of effective interventions including circulatory assist devices. (2) The development of an appropriate animal model of myocardial infarction. Practical and ethical constraint limits the research which can be done on patients with acute myocardial infarction and major disciplines such as biochemistry and physiology are unable to bring some of their most powerful and promising techniques to bear on the clinical problem. There is strong evidence that animal models can be developed which offer the exciting prospect of bringing new and promising disciplines such as myocardial metabolism to bear on the problem of myocardial infarction. (3) The development of improved instrumentation for the study of animals and patients is essential to both of the foregoing activities. A complex system must be developed to permit patient care and simultaneous and non-interfering research. A large number of measurements must be made, stored, analyzed, and presented for this purpose. Several specific instruments need to be modified or developed. (4) A substantial program of clinical pharmacology is needed to establish the true effect of traditional treatment of myocardial infarction and to document precisely the effects of innovations since many forms of treatment including circulatory assist devices will interact in the patient. (5) The largest single mortality group are those patients who die within the hour after the onset of symptoms. Very little is known of the cause of death in these patients but several of the most likely specific causes such as arrhythmias or electromechanical uncoupling might be susceptible to prophylactic or emergency interventions which could preserve life until standard treatment is available.

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 50 participating clinics. Ancillary funds included under Collaborative Research and Development are for reimbursement to other government agencies for performing the required laboratory determinations and for ordering, packaging, and distributing the necessary drugs.

National Blood Resource Program

This program is designed to meet a critical problem that is developing relative to the national resource of blood for therapeutic use. The demand for separate blood components is rapidly rising at a time when there is a lag in the necessary technology to provide them on a large scale. As the demand for whole blood increases moderately with population growth, the demand for fractions of blood for use in specific therapy will rise sharply. Present collection and processing methods of whole blood are costly and cumbersome. In addition, waste of fractions may result from various sources of demand, which would process blood for only their desired component without regard to other component needs.

There is at present no reasonably priced, consistently effective antihemophilic globulin available for treatment of the hemorrhagic crisis of hemophilia. An effective concentrate from blood plasma must be obtained in adequate quantities for further progress in research and treatment. Other fractions of blood needed for research progress and clinical use include: plasma thrombolplastin component for research and treatment of hemophilia B; red blood cells; platelets; separated leukocytes for research in the treatment of leukemia and immunology; complement for immunologic research; and specific protein fractions for highly specialized research and clinical application.

This program, coordinated within the National Heart Institute, will utilize an advisory board representing Government and private organizations concerned with the use of the Nation's blood resource. Blood collection, processing, and utilization programs will be coordinated as closely as possible. The Institute proposes to work through and with the American Red Cross, benefitting from the two agencies' common objectives, the Red Cross nationwide chain of blood centers, and the combined experience and competence developed from past blood research.

The program increase of $1,093,000 in 1968 will further developmental projects which include automation of cellular component separation, research aimed at improving the yield of plasma available for fractionation, and revision of large-scale plasma protein fractionation methods. Low temperature preservation and processing techniques are planned to prevent outdating of blood. Evaluation of

new blood components, and new materials and equipment for component processing will aid progress in clinical research and proper treatment of a diversity of disease entities. Plans for attacking these problems are described in some detail in a special report prepared.

There are also increases of $5,000 for centrally furnished services from the "National Institutes of Health Management Fund".

BIOMETRY, EPIDEMIOLOGY, AND FIELD STUDIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	87	$923,000	87	$920,000	0	−$3,000
Other expenses		667,000		807,000		+140,000
Total	87	1,590,000	87	1,727,000	0	+137,000

INTRODUCTION

This activity is responsible for planning and coordinating the Heart Institute's epidemiological, biometrical, clinical trial, and geographical disease studies in cardiovascular disease in the United States and abroad. Its two primary objectives are: 1) to make use of natural population experiments to carry out epidemiological research to discover what factors may be responsible for unusually low rates of cardiovascular disease found in certain populations in contrast to those factors which may be responsible for the high rates generally found in the U.S.A.; and 2) to determine whether or not the prevention or a reduction of heart disease morbidity and mortality can be accomplished by scientific modification of suspected risk factors in controlled clinical trials.

Program plans in 1967 and 1968

The Framingham Study continues to amass important new data on factors increasing heart disease risk and will be continued on 1967 and 1968.

Two major epidemiological projects, a study of coronary disease and cerebrovascular disease among men of Japanese ancestry in Hawaii and of coronary disease and hypertension among Puerto Rican males, are off to promising starts. These studies are expected to provide crucial testing grounds for a number of hypotheses concerning the role of diet, blood-lipid patterns, and other host and environmental factors as determinants of heart-disease risk.

The program increase of $131,000 will be used in the support of grant related contracts. In 1967 such contracts are mostly to provide uniform synthesis of highly radioactive peptides to grantee laboratories which do not have access to these new peptides because of the high cost involved if they were to be prepared on an individual basis. It is anticipated that this need for peptide production and similar types of grant-related contracts will continue to exist in 1968 to coordinate and utilize the experience of industrial firms to provide grantees with new and unique materials. Included in this net increase is a decrease of $3,000 for one less day of pay in 1968. There are also increases of $9,000 for centrally furnished services from the "National Institutes of Health Management Fund".

DIRECT TRAINING

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	17	$182,000	17	$182,000	0	0
Other expenses		107,000		113,000		+$6,000
Total	17	289,000	17	295,000	0	+6,000

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 pro-

gram 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.

Of the $6,000 net increase requested $4,000 will provide for additional tuition costs and $2,000 for centrally furnished services from the "National Institutes of Health Management Fund".

REVIEW AND APPROVAL OF GRANTS

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	105	$968,000	105	$967,000	0	−$1,000
Other expenses		1,603,000		1,696,000		+93,000
Total	105	2,571,000	105	2,663,000	0	+92,000

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 $92,000 net increase requested $48,000 will provide for additional consultant services. Also included is a net decrease of $1,000 for annualization of positions new in 1967, offset by one less day of pay in 1968. There are also increases of $45,000 for centrally furnished services from the "National Institutes of Health Management Fund".

PROGRAM DIRECTION

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	33	$227,000	33	$228,000	0	+$1,000
Other expenses		591,000		617,000		+26,000
Total	33	818,000	33	845,000	0	+27,000

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 $27,000 net increase requested, $6,000 will provide for additional consultant services. Also included is a net increase of $1,000 for annualization of positions new in 1967 partially offset by one less day of pay in 1968. There are also increases of $20,000 for centrally furnished services from the "National Institutes of Health Management Fund".

NATIONAL HEART INSTITUTE, LABORATORY CLINICAL RESEARCH

New positions requested, fiscal year 1968

	Grade	Annual salary
(3) Scientist	GS-12	$32,781
(2) Research technician	GS-9	15,392
(4) Research technician	GS-7	25,804
Total new positions, all activities (9)		73,977

TUESDAY, APRIL 11, 1967.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. SEYMOUR J. KRESHOVER, DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
HERBERT C. CHRISTOFERSON, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
MRS. FRANCES H. PETTINATO, BUDGET OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	2,504	2,709	2,869
11.3	Positions other than permanent	23	29	29
11.5	Other personnel compensation	28	30	31
	Total personnel compensation	2,555	2,768	2,929
12.0	Personnel benefits	296	318	339
21.0	Travel and transportation of persons	106	120	145
22.0	Transportation of things	19	19	24
23.0	Rent, communications, and utilities	69	85	107
24.0	Printing and reproduction	17	12	12
25.1	Other services	249	257	324
	Project contracts	501	525	629
25.2	Services of other agencies	177	177	200
25.3	Payment to "National Institutes of Health management fund"	1,430	1,404	1,592
26.0	Supplies and materials	343	310	406
31.0	Equipment	217	199	256
41.0	Grants, subsidies, and contributions	17,772	22,215	23,349
	Subtotal	23,751	28,409	30,312
95.0	Quarters and subsistence charges	−6	−5	−5
99.0	Total obligations	23,745	28,404	30,307

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	301	324	331
Full-time equivalent of other positions	4	5	5
Average number of all employees	290	305	320
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	11,180	15,126	15,909
(b) Fellowships	1,442	1,691	1,971
(c) Training	5,150	5,398	5,469
Total, grants	17,772	22,215	23,349
2. Direct operations:			
(a) Laboratory and clinical research	3,777	4,040	4,598
(b) Collaborative research and development	604	711	860
(c) Biometry, epidemiology, and field studies	384	427	435
(d) Review and approval of grants	617	619	662
(e) Program direction	393	392	403
Total, direct operations	5,775	6,189	6,958
Total, program costs, funded [1]	23,547	28,404	30,307
Change in selected resources [2]	198		
10 Total obligations	23,745	28,404	30,307
Financing:			
16 Comparative transfers from other accounts	−263	−151	
25 Unobligated balance lapsing	195	43	
New obligational authority	23,677	28,296	30,307
New obligational authority:			
40 Appropriation	23,677	28,308	30,307
41 Transferred to "Operating expenses, Public Buildings Service," General Services Administration (80 Stat. 674)		−12	
43 Appropriation (adjusted)	23,677	28,296	30,307
Relation of obligations to expenditures:			
10 Total obligations	23,745	28,404	30,307
70 Receipts and other offsets (items 11–17)	−263	−151	
71 Obligations affecting expenditures	23,482	28,253	30,307
72 Obligated balance, start of year	11,182	15,086	20,082
74 Obligated balance, end of year	−15,086	−20,082	−26,288
77 Adjustments in expired accounts	−330		
90 Expenditures	19,248	23,257	24,101

[1] Includes capital outlay as follows: 1966, $164,000; 1967, $201,000; 1968, $256,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $680,000; (1966 adjustments −$1,000); 1966, $876,000; 1967, $876,000; 1968, $876,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. We now have with us Dr. Seymour J. Kreshover, Director of the National Institute of Dental Research. I see we have a biographical sketch of the doctor which we will insert in the record at this point.

(The biographical sketch follows:)

Name: Seymour J. Kreshover.
Position: Director, National Institute of Dental Research.
Birthplace and date: New York, New York, June 22, 1912.
Education:
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.) D. Sc.—1961.

Experience:
1966: Director, National Institute of Dental Research, National Institutes of Health.
1956–1966: Associate Director (In Charge of Research) National Institute of Dental Research, NIH.
1956: Visiting Professor of Dental Research, The Medical College of Virginia.
1956–1960: Associate Trustee, Board of Medical Education and Research, University of Pennsylvania.
1949–1956: Professor of Oral Pathology and Diagnosis, Director of Dental Research, Director of Graduate and Postgraduate Studies, The Medical College of Virginia, Richmond, Virginia.
1946–1948: Private dental practice (part time).
1946–1947: Teaching Fellow in Histoanatomy, New York University.
1946: Chief of Periodontia Clinic, The Roosevelt Hospital, New York City.
1942–1946: U.S. Army Dental Corps, 39th General Hospital (Affiliated Yale Unit)—Chief of Dental Service.
1942–1943: Assistant in Oral Surgery, Yale University School of Medicine.
Association memberships:
American Dental Association (Consultant to Council on Dental Research).
American Medical Association.
Federation Dentaire Internationale.
International Association for Dental Research.
American Association for the Advancement of Science (Fellow).
American College of Dentists (Fellow and Consultant to Committee on Research).
American Public Health Association (Fellow).
Diplomate, American Board of Oral Medicine.
Honorary Member, The New York Institute of Clinical Oral Pathology, Inc.
1961: Chairman, Commission of Dental Research, Federation Dentaire Internationale.
1962: President, International Association for Dental Research.
1963–1966: Secretary, Section Nd (Dentistry), American Association for the Advancement of Science.
Awards:
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.
Publications: Dr. Kreshover is the author of 59 publications.

General Statement

Mr. Flood. Do you have a statement, Doctor? I suppose you would like to proceed with that?

Dr. Kreshover. Yes, I would, Mr. Chairman.

It is a privilege to report to you again on our progress against oral and related disorders.

Since I came before you last year, several events have illuminated the dimensions of these problems and have given new urgency to their solution. One of these is the report from Operation Headstart, which again emphasized the fact that dental ills rank first among children's health problems. Another impetus is provided by the Nation's growing concern that no child be denied necessary dental care.

Last fall, as you know, the Dental Institute, as part of a broad NIH analysis, submitted to the President a detailed report on the magnitude of the various oral diseases, our current activities, and projected plans to cope more effectively with these problems. In preparing this material, we were again struck by the disparity between the total dental needs in this country and the existing level of care. It is apparent that we could not begin to summon the necessary professional and auxiliary

manpower to meet all these needs. Moreover, the economic burden of providing adequate treatment—estimated at $20 to $25 billion for the first year alone—would be staggering. The responsibility inescapably lies with research to provide more effective preventive and control measures.

ANTICARIES TECHNIQUE DEMONSTRATED

For this reason, I am particularly happy to be able to report to you today on successful field trials of a new technique to control dental caries. This disease, you will recall, represents a significant portion of the total problem of oral disorders. For a few minutes each school day, during a 2-year study period, children in a nonfluoridated community wore individually fitted mouthpieces filled with a gel preparation containing 1.1 percent sodium fluoride. Of particular public health interest is that a single dental hygienist, using this method of application, was able to supervise several hundred children—many more than is possible with current techniques of topical treatment. The significant caries reduction, in the magnitude of 80 percent, and the preliminary finding that much higher concentration of fluoride appear in the outer layers of tooth enamel than after conventional methods, provide reason for considerable optimism regarding early utilization of this treatment procedure in community health service programs.

PREVALENCE OF DENTAL CARIES

Mr. FLOOD. What are dental caries?

Dr. KRESHOVER. A lesion now identified as being causally related to certain specific microbial organisms that are incorporated in a soft plaque formation on the tooth surface. The plaque formation on the tooth surface containing these recently identified bacterial organisms——

Mr. FLOOD. This is on the enamel?

Dr. KRESHOVER. Yes. It acts on the carbohydrate substrate material incorporated in the plaque and thereby causes a fermentable process.

Mr. FLOOD. Directly against the tooth itself?

Dr. KRESHOVER. Directly against the tooth. The fermentable process being characterized by the production of acid sufficient in its concentration to cause a dissolution of the hard tooth structure.

Mr. FLOOD. Against the enamel itself?

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. Nothing to do with the gums or the rest of the mouth, but just the enamel of that tooth?

Dr. KRESHOVER. This describes in a very general fashion the process of dental caries.

Mr. FLOOD. Where does it come from? What kind of a bug is it?

Dr. KRESHOVER. The organism is a streptococcus. This organism was first identified some years ago in some early work at the University of Notre Dame in its Laboratory of Microbiology. This was an initial finding which since that time was markedly expanded and illuminated in research conducted at the National Institute of Dental Research by some of our scientists.

Mr. FLOOD. Then it may be infectious?

Dr. KRESHOVER. Yes. Based on studies with germ-free animals—a technique particularly valuable for these kinds of studies—we have been able to demonstrate that the disease of dental caries is indeed infectious and transmissible in the animal model system.

Mr. FLOOD. Where does it come from? How does it arrive on the enamel of a tooth? Here is a tooth, there is nothing on it. Tomorrow morning there is a streptococcus on there. Where did he come from?

Dr. KRESHOVER. As in a variety of other infectious disease processes that other witnesses undoubtedly have and will identify for you in their testimony, this is a disease that interestingly enough harbors in man, so far as we know today, the causative organism. But there are a variety of co-related circumstances that must exist.

Mr. FLOOD. How did it get on that tooth tomorrow morning? How is it transmitted?

Dr. KRESHOVER. The chances are very likely, Mr. Flood, that while I am at the moment, I believe, caries-free and caries-immune, I undoubtedly do harbor the organisms that could cause dental caries.

Mr. FLOOD. Like you do many other organisms.

Dr. KRESHOVER. Yes, sir. There are certain optimum conditions that must be present, namely, the hereditary predisposition to the disease and certain dietary components that act optimally at the present time in order to initiate the disease process.

Dr. SHANNON. The point should be made that the organism is very widely distributed in nature.

Mr. FLOOD. In nature?

Dr. SHANNON. Yes, sir. It is transmissible from person to person via food, via water, via wide variety of media. In other words, as Dr. Kreshover has said, it is not a thing that one has an experience with only occasionally, but rather on a day-to-day basis.

Dr. KRESHOVER. Dr. Shannon raised the important point regarding prevalence and incidence of dental caries, and if I might for just one moment expand on this critical issue to point out that this disease is generally believed to be the most widely prevalent known to man today. It affects children under 2 years of age in the magnitude of some 50 percent. Insofar as our teenage population is concerned, it indeed is very critical. For example, the average 16-year-old has approximately 20 decayed or missing or filled teeth.

Mr. FLOOD. They tell me that when the Job Corps candidates come in at these bases the tooth condition is appalling.

Dr. KRESHOVER. Yes. I will continue, then, Mr. Flood, with my prepared statement at the piont of epidemiologic and genetic studies on page 3, sir.

EPIDEMIOLOGIC AND GENETIC STUDIES

As you know, the problem of dental caries is being attacked on a broad front by the biochemist, the microbiologist, the histologist, and other scientists. As an extension of our laboratory efforts, we are also conducting epidemiologic studies to further clarify the interactions of the three factors responsible for tooth decay: a caries-conducive diet, susceptibility of the individual, and decay-causing germs.

Work done by our scientists and their collaborators has progressed to the point where we can now identify certain types of streptococci associated with caries. But only in the past year, I might add, has

a practical technique been developed for the detection and enumeration of caries-inducing streptococci in the field situation of population studies. A beginning has been made in this epidemiological work by taking samples of dental plaque from the children participating in the fluoride gel study in Charlotte. More extensive studies are planned to determine whether decay-producing organisms are natural inhabitants of the oral cavity in population groups with low caries experience, or whether the organisms must be transmitted to an individual before the disease can be established.

One obstacle to obtaining such data has been the lack in this country of a large, readily accessible group of relatively caries-free individuals. We now have an opportunity for such a study through a grant recently awarded to an American university for the investigation of the geographic pathology of caries. This project will provide for an epidemiologic outpost to be set up at the U.S. Navy's research facilities in Cairo, Egypt, thereby making it possible for investigators to conduct field studies in various areas of the Middle East and nearby Africa. In one such approach, Ethiopians, who have one of the lowest frequencies of tooth decay in the world, will be surveyed before the encroachments of civilization have the opportunity to change this pattern.

While the information emerging from these studies of primitive peoples will fill some serious gaps in our knowledge, concurrent studies in the United States are also valuable in the total spectrum of data, that I might say, will add to our understanding of other oral problems. Among these is a grant-supported study of twins and their single-born siblings which seeks to learn whether heredity or environment exerts the dominant influence in determining oral-facial growth. The role of genes was further clarified by new research data that confirm the similarity among siblings, and in greater degree among twins, of certain types of dental development. In another recent study, however, despite the appearance of a general familial relationship, various aspects of occlusion could not be significantly correlated among siblings.

A related project on dental development draws on a 35-year collection of longitudinal data on somatic, biochemical, and behavioral growth covering three generations, and more than 1,000 individuals. A significant aspect of this latter study is that it permits comparisons to be made between children and their parents at the same age, and explores the effects of matings between people with similar bodily structure and size and those with sharply dissimilar physical traits.

In parallel studies, environmental influences were brought into focus by examination of oral-facial and other birth defects among Negroes and I might say among Caucasians as well. The higher socioeconomic groups were found to have a lower incidence of defects.

The genetic factor in broad racial groups was very much in evidence in an analysis of birth records of over 9,500 American Indians born last year. These infants appeared to be similar to other Mongoloid populations in the number and types of congenital defects. Harelip and cleft palate, in particular, were more common. Studies of a broader segment of the general population indicate that approximately 50 percent of the cases of harelip with or without cleft palate and 25 percent of the cases of cleft palate alone have a hereditary basis.

We hope that research will one day make it possible to provide more precise genetic counseling to members of families with a history of clefts.

In other genetic studies, a hereditary factor in dental caries has been demonstrated for the first time in clinical surveys. Using a recognized genetic marker technique, our investigators found that the ability to taste phenylthiocarbamide is consistently related to the incidence of tooth decay. Thus, tasters of this substance have from 28 to 40 percent lower caries rates in their deciduous teeth.

Genetic studies of this type, as illustrated here, shed much light on the pathogenesis of oral diseases. They and related epidemiological investigations will be given ever increasing attention as research frontiers of unlimited promise.

PERIODONTAL AND BONE DISEASES

Promising work on the relation to periodontal disease of a collagen-destroying enzyme (collagenase), whose discovery in human gingival tissue was reported to this Subcommittee last year, is continuing, together with the further identification of specific causative microbial factors. In addition, earlier and continuing work by the Institute on how fluoride affects the composition and structure of bone has provided a scientific base for current clinical applications in the treatment of osteoporosis, a disease associated with aging, especially in females.

CLEFT PALATE AND SPEECH

Our special report to this subcommittee describes a number of significant advances in improved diagnosis and therapy for cleft palate and its associated speech disorders. As our basic knowledge grows and as corrective techniques are developed and refined, research holds greater assurance that victims of this common birth defect can achieve near-normal appearance and speech. A firm scientific base for these and related studies is being provided by an increasing research emphasis on causative factors, both in laboratory and in clinical-epidemiological investigations.

Mr. FLOOD. We will place the special report you referred to in the record at this point.

(The report follows:)

SPECIAL REPORT: CLEFT PALATE AND RELATED SPEECH DISORDERS

This year, 6,000 new babies will join the ranks of over a quarter of a million persons in the United States born with some form of cleft lip, palate, or both. When there is an opening in the roof of the mouth, nursing care in infancy to permit eating without choking may be only the first of many adjustments to the problem. Usually, surgery is necessary, and often applicances must be specially tailored to close the cleft. Eventually, these procedures, followed by speech training and other forms of medical care, may cost the family from $8,000 to $15,000 before the child's eighteenth year.

Even so, monetary costs are likely to be less burdensome than psychological and social difficulties. To some quarter of a million cleft victims in this country and their families, lifelong, nagging questions are: What caused this? What can we do to make life as productive, and communication as normal, as possible? Answers to such questions are a continuing concern of the National Institute of Dental Research. Through extensive research, which the Institute conducts in its laboratories in Bethesda and supports in various universities

and other institutions, significant progress is being made in understanding the causes, treating, and ultimately preventing this defect.

DEFINITION OF CLEFTS

Long before birth, the tissue components that develop into the mouth and palate begin to form. Gradually, these bilateral structures turn towards each other like shelves and eventually fuse in the center. In this way the nasal cavity is separated from that of the mouth. When fusion is incomplete, the result is a cleft. Palates may join while lips do not, producing the harelip. Also, palates may be incomplete, but the lips may be perfectly formed. Again, both may fail to meet. Variations in the turning and joining process may leave small pits in the lip, or palatal defects so slight as to require special methods of inspection for diagnosis. These "microforms" of cleft palate are sometimes found in members of the family of a person with a frank cleft.

CAUSES OF CLEFTS

The precise causes of these birth defects are unknown. Cleft is an umbrella word covering a group of defects. Some of these look alike but appear to have entirely different causes. Heredity is clearly a factor in some clefts, while environment takes precedence in others, and sometimes, compound causes are suspected in which environmental hazards seem to trigger clefts in genetically susceptible individuals. Past studies of identical twins show that when one has a harelip, with or without a cleft palate, the other develops a defect in only forty percent of the cases. Whereas, when one develops a cleft palate alone, the other shares the defect in only about ten percent of the cases. It appears that research findings about cleft palate are not necessarily applicable to cleft lip or vice versa. As causes become better known, progress towards prevention will increase. Meanwhile, research must explore a variety of apparently unrelated leads.

The role of hereditary factors has been studied through large-scale studies of races and special population groups. The highest frequency of cleft palate known in man occurs in North Carolina. Forty-two cases were found in a socially isolated, somewhat inbred, tri-racial population of approximately 4,000. Information about this group is still being analyzed in the hope of learning more about the distribution of cleft palate and other associated defects.

The incidence of clefts is one aspect of an ongoing study of American Indians born in Public Health Service facilities. Examination to date of some 20,000 birth records by Institute scientists has revealed a high frequency, which is characteristic of races of Mongolian derivation. Caucasians generally have fewer clefts than orientals, but considerably more than Negroes. Further studies of these differences will help clarify the relative role of genetic and environmental factors.

An interaction of racial and socio-economic factors is indicated by grant-supported research at Howard University. An analysis of records of some 80,000 Negro births in two Washington, D.C. hospitals over a ten-year period showed that more clefts of all types, as well as other birth defects, appeared in the hospital serving the lowest socio-economic group.

Institute geneticists, in collaboration with scientists at the Lancaster Cleft Palate Center, are studying families with children having cleft palates. Their findings support the theory that the production of harelip is influenced by multiple genes in those cases where inheritance is a factor. On the other hand, in suspected genetic cases of cleft palate without harelip, a single gene often seems to be the culprit. This gene usually is not sex-linked and, though dominant, frequently does not express itself visibly. Geneticists consider that heredity plays a major role in about one half of the cases of harelip with or without cleft palate and in approximately one quarter of those with cleft palate alone.

There is also evidence that changes in the environment which occur at critical periods during prenatal development can cause clefts. Institute studies of animals with experimentally produced cleft palates support the theory that the defect may be caused by various factors acting through different channels. For example, one can produce cleft palate at will by giving compounds such as chlorcyclizine in large doses at a critical time to pregnant rats. This drug interferes with the normal process in the embro which turns the two shelves of palatal tissue into a horizontal plane so that they can fuse. Institute scientists have shown the specificity of this action of chlorcyclizine by neutralizing

it with a structurally related compound, homochlorcyclizine. When the latter is given first, few clefts appear even though cholorcyclizine is administered in the dosage schedule which usually produces defects.

Vitamin A, in doses much larger than those used in clinical treatment, also impairs metabolic processes in the rat, causing a general disruption of embryonic development in the facial region.

Seeking more clarification of these processes, the Dental Institute is supporting studies of the effects of organic compounds in animals that more closely resemble man. The recent discovery of spontaneously occurring cleft palate in monkeys is encouraging to those trying to identify the precise mechanisms determining the formation of face, mouth, and palate in the human embryo.

In another approach, development of a patient's individual teeth is compared with norms described in a timetable of tooth development, such as that recently published by the University of Pittsburgh. Since certain tooth abnormalities are often associated with clefts, it may be possible to establish a calendar pinpointing the occurrence of a prenatal disturbance causing both defects.

DIAGNOSIS AND DESCRIPTION

All palatal defects do not necessarily express themselves as malformations. The function may be poor, even though the palate appears normal. In one type, the cleft is difficult to discern and the palate is somewhat underdeveloped. The patient with this condition, however, also lacks part of the neural equipment essential for guiding the tongue in articulation. This loss of function explains the speech difficulties of some individuals.

The motions of speech and associated breathing are being studied at several cleft-palate centers supported by the Institute. Studies at the University of North Carolina have shown that some individuals with incompetent palates take less time than normal subjects to build up intra-oral air pressure in order to reduce the release of air through the nose. This factor probably contributes to the omissions and distortions of consonants that are often heard in cleft-palate speech.

Investigators are paying much attention to the motions of the soft palate and the back wall of the throat. These parts, termed the velopharynx, must be able to meet to close off the upper part of the pharynx, so that the breath stream may be diverted through the mouth for normal, non-nasal speech.

To visualize movements of soft-tissue structures during speech, Duke University scientists have developed an improved cinema X-ray technique. Cineradiographic equipment is mounted so that it can be rotated in a full circle around the patient to produce a three-dimensional picture of nose and throat without some of the problems involved in ordinary stereoscopy. A tape recording of the speech is synchronized with the moving picture unit so that movements and sound can be studied together.

The motions necessary for normal speech have been precisely defined with a computerized model by investigators at the University of North Carolina. They report that when the velopharyngeal mechanism fails to close by as little as two millimeters, or about one-sixteenth of an inch, speech distortion may occur. These observations are confirmed by clinical research at the University of Kansas.

PROBLEMS AND ADVANCES IN CLEFT PALATE THERAPY

Unintelligible or distorted speech can now be largely avoided by special training to correct nasal tones and poor articulation. To achieve further improvement, investigators are seeking reliable standards for evaluating different methods of speech training. Also under consideration is the question of the best timing of speech training in relation to the use of surgery, mechanical devices, and other kinds of treatment for closing the cleft.

A team at the University of Kansas follows a flexible program of testing various methods in hope of avoiding the need for secondary surgery to improve speech. Related studies at the University of Iowa show that when there are anatomic reasons for speech difficulty, speech training before surgical correction can lead to psychological problems and the formation of faulty speech habits that are hard to correct even after surgery. These investigators consider that speech training is most effective following correction of structural defects in the palate.

However, artificial appliances may be used to cover the cleft. While, in the past, these obturators were often kept in place permanently, like dentures, today they mainly serve an intermediate purpose preceding surgery. Speech specialists at the University of Kansas have developed tests to evaluate how these treatment

methods affect speech. A speech simulation test developed at the University of Iowa is also used for evaluation. In some children who can almost close the gap, a small plastic exerciser placed against the soft palate may help the youngster develop and retain the ability to direct his breath through his mouth instead of his nose. A small bulb held close to the soft palate by an obturator can do the same thing. As the child learns control, the bulb is gradually made smaller, and eventually may be removed.

Often surgery is necessary to lengthen the palate, bridge the gap, or otherwise repair the defect. Recent studies at Iowa have shown the depth of the nasopharynx can be as important to intelligible speech as the length of the soft palate. Techniques are now being developed to improve palate surgery by reducing this depth.

Last year Stanford University surgeons reported encouraging results with a modification of a surgical procedure called the "combined pushback and pharyngeal flap operation." To date, forty-seven patients have been operated on in this way, and more than half have attained almost or completely normal speech within two years. With the exception of one patient with a paralyzed palate, the others are markedly improved, but need to be evaluated longer than one year after surgery.

In another type of operation reported at Stanford, cartilage or a synthetic material is inserted in the back of the throat at the level of the palate. The implant makes closure easier by narrowing the gap between the soft palate and the wall of the pharynx. Both rib cartilage and synthetic implants (silastic) give immediate and dramatic results.

In addition to this procedure, bone-grafting studies conducted at Duke University promise improvements in cleft-palate therapy. Bone grafts in patients ranging in age from six months to thirty-four years have been observed for study periods up to four years. Surgeons report a higher rate of successful treatment than is usual for difficult cases of bilateral clefts. Also, in unilateral clefts, the use of bone grafts reduces the number of treatments required.

Methods measuring physiological action are used to evaluate the success of cleft palate surgery. At the Eastman Dental Center, normal limits of oral and nasal air pressure and air flow have been determined. Preliminary comparisons of these factors in cleft palate patients before and after surgery show that measurements of intra-oral pressure and, to a lesser extent, nasal air flow during speech can definitely indicate the success or failure of the operation.

A continuing question in cleft-palate therapy has been whether or not surgery disturbs facial growth. A study of twenty-one cleft patients, each followed from six months to seven years by Institute scientists, showed no evidence that current practice in plastic surgery under the best conditions inhibits growth. More than half of the children had their palates repaired before they were two and a half years old.

In addition to having speech difficulties, children with clefts are frequently unable to hear well. Hearing loss may result from infection by bacteria that can easily pass from the mouth through the cleft into the nose and from there through the eustachian tube into the ears. Also, when the eustachian tube is not sufficiently open to let air through easily, the ear drum is affected and fluid is likely to collect in the middle ear. Duke University surgeons report that of fifty children, 14 to 18 months of age, whose adenoids were removed then their palates were repaired, none has developed an ear infection, and half of them, now four years old, hear normally. Physicians at the University of Iowa report that silicon rubber tubes inserted in the eustachian tubes of children with frequent ear infections, seem to relieve the ear drum in a number of cases.

The teams of dental, medical, speech, and other specialists supported by the Institute in a number of cleft-palate centers have not only improved the care of individual patients, but have also increased the general understanding of cleft palate and its impact on the family. It has been learned, for example, that after a child with a cleft learns to talk normally, he talks less than other children. According to studies at the University of Pittsburgh, these youngsters generally appear to be less spontaneous and creative. To explain this finding, psychologists will study the interactions between these children, their parents, and their brothers and sisters. Perhaps family relationships may be affecting expressive speech and creativity.

As a part of its effort to inform the public about cleft palate and the research into its causes and treatment, the Dental Institute has published a new booklet for general distribution. It describes clefts and the difficulties they cause, and advises parents to seek specialized clinical aid for their children since so much can be done to help them live normal, useful lives.

ORAL SENSATION AND PERCEPTION

One aspect of facial deformity that we know little about is the problem of improper sensory-motor integration. Gradually, however, new insights are emerging from the collaborative program on oral sensation and perception begun by the Institute in 1964. A significant contribution was the recent publication of a report on major studies in this complex field, as well as guidelines for future investigators.

Institute and grant-supported scientists, who earlier had shown that the ability of the mouth to feel is related to its efficiency in swallowing, speech, and respiration, have now devised clinical experimental methods to evaluate oral tactile sensory function. One of these methods tests the ability of the tongue to recognize various contours and shapes. This procedure, in which children as young as 4 years of age can cooperate, simultaneously evaluates developmental progress in both the mouth and the brain.

ORAL CANCER

Studies or oral cancer are seeking to detect the precancerous state early enough to be able to abort the developing cancer. Grant-supported work is substantiating that certain conditions in the mouth may lead to oral cancer. Accordingly, increasing emphasis is being given by epidemiological, clinical, and laboratory studies to the characterization of precancerous lesions, the better understanding of predisposing and etiological factors, and an assessment of exfoliative cytological techniques for diagnosis.

BIOMATERIALS

Collaborative efforts between the Dental Institute, the National Bureau of Standards, various industrial laboratories, and other research organizations are providing a valuable base of knowledge on the chemical and physical properties of synthetic and biologic materials and their interactions with the oral environment.

Special attention is being directed to the development of improved restorative materials with adhesive bonding properties. In one proposed approach to this problem, the study of natural cements produced by marine plants and animals, such as the barnacle, appears to offer a particularly promising line of pursuit.

You might be interested in an aside to recall the barnacle has the ability to harden underwater, it can resist temperature change and stress and it is remarkably enduring. So this line of attack is one that we have great ambition for.

In a related study scientists using a silane adhesive have been able to fasten porcelain teeth to denture bases successfully without pins. By pins I talk about the metallic inserts that unite the two structures.

It is estimated that this procedure will save $8 million annually in precious metals. In other grant-supported work, plastic teeth implanted in baboons for study periods of up to 5 years continue to be retained with effective function, a study, I might add, that was of great interest to your predecessor, Mr. Fogarty, inasmuch as this research is being conducted at Brown University.

We are very gratified at the support that has made it possible to begin the development of several dental research institutes as centers of excellence in the sciences related to oral health.

RESEARCH CENTERS

My text is changed slightly here and I will state it as follows: So far this fiscal year two applications have been approved and funded for the respective planning and development of research centers at the University of Washington in Seattle and the University of Pennsylvania in Philadelphia. Others are also being negotiated for similar planning or developmental phases of research institute support in the current and the next fiscal year. We feel that this program should continue to go forward in view of its present potential contributions and the considerable interest which it has demonstrated. These institutes will bring to bear on oral health problems the diversified resources of a research and educational complex.

The resources of a single university may be used, or the proposed center may draw on resources available within a region. We view these centers as pooling the knowledge and skills of not only the traditional healing arts but also the broader biological sciences, the behavioral and social sciences, and the engineering and other physicochemical sciences. Through these intensified, coordinated attacks on oral diseases, knowledge of their causes, prevention, and improved treatment will increase rapidly.

ORIGIN AND DEVELOPMENT OF DENTAL INSTITUTE'S PROGRAMS

I believe, Mr. Flood, that the next item appearing in my opening statement might best be prefaced by a few remarks that would introduce it more appropriately and with your permission and that of your associates I wonder if I may be privileged to depart from the text and indicate that thus far in my opening statement I have pinpointed by example those major elements of our program that, in receiving emphasis both via our intramural and extramural research programs, are moving forward with evidence of significant accomplishment and, hopefully, provided you and your associates with a sense of purposeful and productive movement with respect to our programs.

In this regard I believe that our strides to date in developing a strong and sound scientific base for dentistry and for projecting our needs for the future can be better appreciated if I reviewed most briefly the origin and development of the Institute's programs. For example, we first can identify dental research activities within the U.S. Public Health Service as far back as 1931, with the organization of the so-called Dental Hygiene Unit staffed by a single dental officer by the name of H. Trendley Dean, who is, I imagine, well recognized by name as the person principally responsible for the development of fluoridation as we see it today. In 1931, therefore, the programs were largely directed toward applying the principles of epidemiology to community studies of mottled enamel, and this rapidly expanded so that in 1938, as an underpinning for this effort in community studies, it became apparent that one must become involved in laboratory endeavors. So we had then the beginnings of pathology and biochemistry and physiology and the like as an essential component of dental programs within the Public Health Service.

In 1948, principally in recognition of the high standards of research undertaken by the dental hygine unit, the Congress enacted legislation which established the National Institute of Dental Research. At

that time it had a complement of 12 professional workers. In a period of 10 years this expanded to 40 professional workers, and it shortly thereafter became involved in the conduct of extramural programs. I will comment on this most briefly with respect to manpower. Today, the Institute professional staff has more than doubled. The contributions that this limited but most vigorous manpower pool made possible were, as examples, new understanding of the bacterial causes of dental caries and periodontal disease and other conditions; new knowledge about the causes of oral ulcerations that are so troublesome to us; and better understanding of the complex interplay of genetic and environmental factors in oral facial malformations.

MANPOWER PROGRAM

Again we turn to our manpower program and recognize the fact that with the rather meager resources at the time in fellowships and training grants, we were supporting in 1958 approximately 60 people in university environments.

Today we have in training approximately 600 promising young men and women. This 600 makes it possible for us to turn out in the range of 200 each year. While this is quite gratifying we nevertheless can anticipate that in the course of the next 10 years, as you and Mr. Laird in earlier discussions this morning pointed to the importance of projecting ahead, we will have, at the very minimum, approximately 10 new dental schools. I would also call to mind, Mr. Flood, that we are engaged not only in the training of researchers but our researchers are indeed the academicians that must staff our teaching facilities. They do a two-pronged job in this regard. It is our estimate that in the course of the next few years, between now and possibly 1973, we must double our output of people trained in the dental sciences, to occupy these important posts in teaching institutions and research institutions.

Our manpower solutions, then, relate not only to a bolstering of our training and fellowship programs in the years ahead, but to providing environments whereby the dental sciences and dental institutions might be able to attract from our large manpower pool of of Ph. D. trained workers, a satisfactory number to add to our talents and our responsibilities. A rather worrisome statistic might be called to your attention. I had an opportunity to search this out just the other day in examining the complement of Ph. D.'s represented on the full-time faculties of our medical schools versus our full-time faculties in our dental schools. The medical school full-time faculty today is in the range of some 8,600 or 8,700, and represented among this complement of teacher-investigators there are approximately 30 percent with Ph. D.'s. On the other hand, if we look at our 49 existing dental schools with a grand complement of something approaching 1,600 full-time teachers, our Ph. D. complement is only in the range of 12 percent. Obviously we have a job to do not only in improving our environmental situation in existing institutions but also to train more people in the fundamental sciences.

In our view, then, the Institutes that this committee made possible through its recommended appropriation of $3 million in our 1967 budget, would do much to change this picture. It will add, or they

will add, rather, a new dimension to dental research by engaging the broad base of the universities and a rich cross fertilization and interaction of various disciplines. In this way we believe we will add to the dental environment and to the solution of dental problems, the knowledge and skill of a variety of personnel trained in the basic biological and other life sciences who are not now located in institutions engaged in dental research. For these activities, and anticipating our needs for fiscal 1968, a budget of $30,307,000 is before you as compared with $28,404,000 for the current fiscal year, representing an increase of $1,903,000. The increase will permit us to expand those areas of laboratory, clinical, epidemiological and applied research where needs and opportunities are greatest for productive work. I would be very happy to do my best to answer any questions you and your associates might have.

SUMMARY OF BUDGET REQUEST FOR NATIONAL DENTAL INSTITUTE

Mr. FLOOD. What we call the adjusted appropriation for 1967 is $28,447,000 and the request for 1968 is $30,307,000. That is an increase of $1,860,000.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. If that is so, you must have stretched your imagination a little to try to show that this would cover more than the increased costs. For instance, you indicate you can finance eight more research projects, two more training grants and seven more positions.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. These are pretty small, but do you really think that even those small increases are possible?

Dr. KRESHOVER. We, of course, needless to say, must do our best. We believe that with the establishment of certain priorities we can keep our program with a sense of mobility, of not standing still. While in certain areas this might indeed be difficult to accomplish, as you have perceived, we do feel it absolutely urgent that we keep our program moving ahead.

Mr. FLOOD. Yes, I am sure you do. That is very commendable. I am wondering how are you going to do it? What are you going to use for money? This is only a 6-percent increase. Increases in the cost of maintaining the same program level are estimated by many experts to be more than that.

Dr. KRESHOVER. I am rather speechless to try to respond adequately to this.

Mr. FLOOD. What about this man here? What do you think?

Mr. CHRISTOFERSON. Mr. Flood, this will mean in the field of research grants that we will not be able to fund as many grants as would be approved by the Research Council, among other things. This will also be true in the field of training.

Mr. FLOOD. You have to make a hard choice.

Dr. KRESHOVER. Yes, we indeed will. We are rather optimistic that a recasting of some of our programs in the context of broad gaged dental research institutes might make some impact on this objective.

UNIVERSITY-BASED RESEARCH INSTITUTES

Mr. FLOOD. Last year we gave you $3 million above the budget to set up these six university-based research institutes.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. What about your plans for 1968?

Dr. KRESHOVER. The $3 million was a line item in our 1967 budget. As I indicated to you earlier, we have now approved and have funded two such grants.

Mr. FLOOD. That is Washington and Pennsylvania.

Dr. KRESHOVER. That is correct. The remaining three that will be considered at the next Council meeting have only thus far been reviewed in our so-called primary review mechanism. I believe it would be inappropriate for me to identify these universities. But nevertheless there are three more that we anticipate are of such quality that they will be recommended for approval and indeed will be negotiated for funding in the current fiscal year. These will be carryovers as five full-fledged institutes under varying stages of development or planning for 1968, and during the forthcoming fiscal year we anticipate funding one additional institute with the $3 million that is being requested for fiscal 1968.

GERM FACTOR IN TOOTH DECAY

Mr. FLOOD. You remember last year we spent some time telling you of our interest in research on the germ factor in tooth decay and urged that you vigorously pursue it.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. Is this what we talked about earlier?

Dr. KRESHOVER. Yes, Mr. Flood.

Mr. FLOOD. There is no other germ factor?

Dr. KRESHOVER. I should point out that while I emphasized a specific causative organism in my earlier comments, the likelihood is that similar approaches to our research objectives might well identify additional organisms that might be causally related not only to dental caries, but other diseases as well.

Mr. FLOOD. What advance have you made in a year? We urged you to get into this thing and expressed an interest. Have you advanced or are you just digging away?

Dr. KRESHOVER. No, sir; we have advanced significantly. We can now demonstrate in selected population groups a specific causative organism in man, which now suggests for the first time that a similar process of decay, of the development of the caries lesion, exists in man as it does in the experimental animal model system.

INCIDENCE OF DENTAL CARIES RELATED TO CIVILIZATION

Mr. FLOOD. On page 9 you say:

> The world-wide incidence of dental caries ranges from nearly 100 percent in this country to essentially zero in some primitive areas.

I think you mentioned Ethiopia especially.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. How much do we know regarding the reasons for this? Why would that happen? You say you want to get into Ethiopia before the encroachment of civilization?

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. How much do we know regarding this problem among peoples?

Dr. KRESHOVER. We know that dental caries is a complex disease as is periodontal disease; being a complex disease, we recognize the fact that more than one factor certainly comes into the causative range. We know that diet, we know that hereditary factors, we know that exposure, possibly, to those with the disease might indeed excite the disease in man.

We have had evidence in a study done some few years ago in Alaska that as the inroads of civilization took place, tooth decay increased, whereas before that time caries was practically non-existent, as it is today in Ethiopia. The inroads of civilization have changed that pattern remarkably.

Dr. SHANNON. I think one might make the point—if Dr. Kreshover had not I was going to—of the transition of the Alaskan Eskimo beyond the less civilized characteristics of some Ethiopians.

If one made an epidemiologic study of this condition one would see that one of the major changes is this behavior pattern. The basic problem, as far as it has been studied in the Alaskan Eskimo, relates much more to dietary habits than to others. As Dr. Kreshover has pointed out, this is a very complex relationship of many factors—so complex that one must get population isolates that are quite different.

FLUORIDATION

Mr. FLOOD. Are there any new findings regarding fluoridation of water supplies?

Dr. KRESHOVER. Perhaps the most significant development over the course of the past year is the new technique I alluded to earlier whereby fluoride can be applied topically in a form that would provide a benefit to the child, and our experiment has been largely limited to children up to this time, in the range of some 80-percent reduction in dental caries. The other significant development with respect to fluoride, to depart momentarily from the dental caries story, is the benefit that it presumably has, according to the best evidence to date, in the attack on periodontal disease.

We have found, for an example, in communities that had been following a regimen of fluoridation for some years, that not only is there a beneficial effect on dental caries, but also in the reduction of the incidence of periodontal disease. We have found also—and when I say "we" I talk now more broadly——

Mr. FLOOD. What do you mean by periodontal?

Dr. KRESHOVER. Periodontal disease is an inflammatory lesion of the supporting structures of the teeth, extending beyond the superficial gum tissue, causing breakdown of the underlying membrane structures and the underlying bone which normally holds the teeth in their sockets.

I might point our furthermore in our consideration of the fluoridation effort today that there are currently being benefited across our United States of America in the range of some 60 million people in over 3,000 communities. In addition to this total there are another 7 million who are residing in areas that are naturally fluoridated.

Mr. FLOOD. What would be the source of the natural fluorides in the water?

Dr. KRESHOVER. The natural mineral content.

Mr. FLOOD. What would they be?

Dr. KRESHOVER. The many fluoride-bearing soil minerals that come in contact with drinking water supplies.

REFERENDUMS ON FLUORIDATION

Mr. FLOOD. Did you lose any converts?

Dr. KRESHOVER. Through 1966, counting all years up to that time, the total number of referendums held in the United States were 952. The total won was in the range of 40 percent; the total lost, 60 percent. This is broken down further, if you care to have these other figures, to the number of referendums to adopt fluoridation, and the number to continue, and the number to reinstate. Would you want these figures?

Mr. FLOOD. Yes.

(The information follows:)

Number of referendums to adopt fluoridation	821
Total won (40 percent)	336
Total lost (60 percent)	485
Number of referendums to continue	100
Total won (35 percent)	35
Total lost (65 percent)	65
Number of referendums to reinstate	31
Total won (50 percent)	15
Total lost (50 percent)	16

Mr. FLOOD. Why would you lose a fight like that?

Dr. KRESHOVER. Presumably the Public Health Service still has a real challenge ahead to educate our people. The populations in our major cities must be educated to the fact that fluoride has beneficial aspects, and that the scares that have been rather abundant are, nevertheless, we hope, diminishing today and are ill-founded.

Mr. FLOOD. What are some of the worst scares? What are some of the worst indictments? Here is the Public Health Service that says you should have this for the benefit of your children's teeth. Why would anybody want to debate that? What is the point? What are they afraid of?

Dr. KRESHOVER. The interesting thing about this is that the professional judgment is sound, and by "professional judgment" I refer now not only to the Public Health Service, but also to the American Dental Association, the American Medical Association, the American Public Health Association.

Mr. FLOOD. What are they afraid it will do?

Dr. KRESHOVER. The concerns have been so wide ranging.

Mr. FLOOD. Then you should have no problem giving me two or three. What are the two most alarming things that you are supposed to be doing to people with this?

Dr. SHANNON. I think I would like to answer that question. The concerns come under two groups. In the first group of concerns, fluorides are presented as a potentially toxic substance that can have dire consequences to health, indeed, in isolated biological systems with very high concentration such toxicity can be shown to obtain. I am talking now about the test tube. In the oral ingestion of one part per million this is ridiculous. Related to this concern of toxicity are alarming things ranging from a number of diseases, actually, to the fear of

the production of cancer. The other general series of concerns relate to whether indeed it is a public responsibility to impose the will of the community upon the individuals that reside in the community or whether the individuals should have the right to elect to have fluoride or not.

So the grouping of opinion is around these two very broad issues. The first is a wholly fallacious one in that it has no scientific basis. Much the same way, for example, there have been arguments or there were arguments earlier in the century when one started to chlorinate water. A substantial group of people felt they should have a right to determine whether their individual water supply should be chlorinated or not. There it was possible to show that the public good was at stake here because the lack of chlorination could indeed result in epidemic disease. It was a little easier to demonstrate public good there than in the case of fluorides in relation to dental caries. Again the falacious concept of toxicity and the imposing of the community will on the individual are the two centers of opposition to fluoridation.

Mr. FLOOD. Mr. Natcher.

TRANSPLANTATION OF TEETH

Mr. NATCHER. Doctor, do you have underway at this time a program concerning the replacement of teeth that have been drawn or pulled? I don't know the terminology for it.

Dr. KRESHOVER. Extracted.

Mr. NATCHER. What are you doing along this line?

Dr. KRESHOVER. We are undertaking today, largely through grant supporting mechanisms, studies of a variety of reconstructive materials used to replace or repair structures lost as a result of dental disease or oral facial disease. These are largely limited to categories of restoring decayed teeth for obvious need, replacing of lost teeth, and repairing facial defects from either congenital malformation or from injury. Our research is largely directed toward the development of new and improved materials with adhesive bonding properties.

Mr. NATCHER. Doctor, pardon me for interrupting you.

Dr. KRESHOVER. Yes, sir.

Mr. NATCHER. You have a tooth that is broken and you have to remove it and it is a good tooth.

Dr. KRESHOVER. Yes, sir.

Mr. NATCHER. Can you place a tooth back in that socket at this time? Does it have to be done immediately? What are you doing along that line? That is what I have in mind.

Dr. KRESHOVER. I see. What you are alluding to now is what we would call the transplantation or the implantation of teeth.

Mr. NATCHER. That is the part I am interested in. What are you doing about that?

Dr. KRESHOVER. I would say first the replacement of damaged or lost parts of tissues or organs in man, generally speaking teeth and other structures, from other humans or lower animal forms has been a long continuing chapter of interest and challenge in the history of the dental sciences as well as in the broad range of the biomedical sciences. The principal obstacle to advance has seemingly been rather insurmountable; a barrier insofar as the immunological response or

rejection of the individual to this foreign material is concerned, whether it be the tooth that was extracted and then replaced in the same person, the so-called autogenous implant or transplant, versus the implantation from another subject of the same species, a so-called heterogenous transplant. The greatest impetus to our current progress has been the collaboration between the immunologist, the dental scientist, the biochemist, the wideranging numbers of scientific disciplines that can all pool their talents and hopefully come up with a material that would surmount this barrier of an immunological or rejection response. The Hodash study referred to earlier at Brown University is one whereby they use a polymer structure, a material that would reproduce in anatomical form the tooth that has been lost.

This is replaced in the socket of the individual or the animal that has lost its natural tooth.

As of this time, using principally the baboon, the success has been quite remarkable. We hope that in the early years ahead, and possibly even as early as the next fiscal year, trials might be made on the human subject; carefully controlled studies whereby this technique might be proven to be applicable to man.

Mr. NATCHER. Thank you, Doctor.

Mr. FLOOD. Mr. Casey?

Mr. CASEY. I have no questions.

Mr. FLOOD. Thank you very much.

Dr. KRESHOVER. Thank you, Mr. Chairman.

JUSTIFICATION MATERIAL

National Institute of Dental Research

Amounts available for obligation

	1967	1968
Appropriation	$28,308,000	$30,307,000
Transfer to "Operating expenses, Public Buildings Service," General Services Administration	−12,000	0
Comparative transfer to "Salaries and expenses, Office of the Secretary"	−91,000	0
Comparative transfers within NIH	+242,000	0
Total	28,447,000	30,307,000

Obligations by activities

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$15,126,000		$15,909,000		+$783,000
General research support grants		(1,079,000)		(1,294,000)		(+215,000)
Scientific evaluation grants		(42,000)		(42,000)		(0)
Categorical clinical research centers		(400,000)		(400,000)		(0)
Dental research institutes		(3,000,000)		(3,000,000)		(0)
Fellowships		1,691,000		1,971,000		+280,000
Training		5,398,000		5,469,000		+71,000
Direct operations:						
Laboratory and clinical research	232	4,040,000	238	4,598,000	+6	+558,000
Collaborative research and development	3	711,000	4	860,000	+1	+149,000
Biometry, epidemiology, and field studies	23	427,000	23	435,000	0	+8,000
Review and approval of grants	40	619,000	40	662,000	0	+43,000
Program direction	26	392,000	26	403,000	0	+11,000
Total obligations	324	28,404,000	331	30,307,000	+7	+1,903,000
Unobligated balance, reserve	0	43,000	0	0	0	−43,000
Total obligations and balance	324	28,447,000	331	30,307,000	+7	+1,860,000

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Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	324	331	+7
Full-time equivalent of other positions	5	5	0
Average number of all employees	305	320	+15
11 Personnel compensation:			
Permanent positions	$2,709,000	$2,869,000	+$160,000
Positions other than permanent	29,000	29,000	0
Other personnel compensation	30,000	31,000	+1,000
Total personnel compensation	2,768,000	2,929,000	+161,000
12 Personnel benefits	318,000	339,000	+21,000
21 Travel and transportation of persons	120,000	145,000	+25,000
22 Transportation of things	19,000	24,000	+5,000
23 Rent, communications, and utilities	85,000	107,000	+22,000
24 Printing and reproduction	12,000	12,000	0
25 Other services	257,000	324,000	+67,000
Project contracts	525,000	629,000	+104,000
Services of other agencies	177,000	200,000	+23,000
Payment to "National Institutes of Health management fund"	1,404,000	1,592,000	+188,000
26 Supplies and materials	310,000	406,000	+96,000
31 Equipment	199,000	256,000	+57,000
41 Grants, subsidies, and contributions	22,215,000	23,349,000	+1,134,000
Subtotal	28,409,000	30,312,000	+1,903,000
Deduct quarters and subsistence charges	5,000	5,000	0
Total obligations by object	28,404,000	30,307,000	+1,903,000

Summary of changes

1967 enacted appropriation	$28,308,000
Transferred to "Operating expenses, Public Buildings Services," Administration	−12,000
Comparative transfer to "Salaries and expenses, Office of the Secretary"	−91,000
Comparative transfers within NIH	+242,000
Unobligated balance, reserve	−43,000
1967 total estimated obligations	28,404,000
1968 estimated obligations	30,307,000
Total change	+1,903,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built-in: Annualization of new positions authorized in 1967	10	$218,000		$18,000
B. Program:				
1. Research grants		15,126,000		783,000
2. Fellowships		1,691,000		280,000
3. Training grants		5,398,000		71,000
4. Laboratory and clinical research	232	2,982,000	6	388,000
5. Collaborative research and development	3	707,000	1	147,000
6. Biometry, epidemiology and field studies	23	396,000		6,000
7. Review and approval of grants	40	437,000		23,000
8. Program direction	26	263,000		7,000
Total program increases			7	1,705,000
Payment to "National Institutes of Health management fund" for centrally furnished services:				
Laboratory and clinical research		1,058,000		159,000
Collaborative research and development		4,000		2,000
Biometry, epidemiology and field studies		31,000		2,000
Review and approval of grants		182,000		21,000
Program direction		129,000		4,000
Total management fund increases				188,000
Total increases			7	1,911,000
DECREASES				
1 less day of pay in 1968 (total decreases)				−8,000
Total net change requested			+7	+1,903,000

EXPLANATION OF CHANGES

Research grants—The increase of $783,000 includes $215,000 for general research support grants, $288,000 for noncompeting requirements of the regular program and $280,000 for competing projects.

Fellowships—The increase of $280,000 will provide funds for 25 additional awards.

Training—The increase of $71,000 will provide funds for 2 additional grants in the dental graduate program.

Laboratory and clinical research—The increase of $388,000 and 6 positions will allow for expansion of research in dental caries and oral and related diseases.

Collaborative research and development—The increase of $147,000 and one position will allow for expansion of research and development of an adhesive dental restorative material.

Biometry, epidemiology and field studies—The increase of $6,000 will support increased operating expenses.

Review and approval of grants—The increase of $23,000 will support increased operating expenses.

Program direction—The increase of $7,000 will support increased operating expenses.

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.

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

	1967 estimate	Purpose
Transferred to "Operating expenses, Public Building Service," General Services Administration.	−$12,000	Transfer of rental costs to GSA.
Comparative transfer to "Salaries and expenses, Office of the Secretary".	−91,000	Transfer of invention and patent activities.
Comparative transfer from: Transfers within NIH.	+242,000	Redistribution of the NIH management fund.

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$10,605,000	$11,173,000	+$568,000
Special programs	4,521,000	4,736,000	+215,000
Total research grants	15,126,000	15,909,000	+783,000

PROGRAM PLANS FOR 1967 AND 1968

The regular program will support approximately 300 research projects in more than 100 institutions during 1967 and 1968. The increase includes $288,000 for non-competing continuation grants with the remainder, $280,000, being allocated for competing grants.

Dental Caries and Hard Tissue Studies

There is a critical need for extensive epidemiological studies of factors responsible for variations in the worldwide incidence of dental caries, ranging from nearly 100 percent in this country to essentially zero in some primitive areas. Research on the geographic pathology of tooth decay should help clarify the role of streptococci, as well as the interaction of dietary and genetic factors, in human caries.

Factors affecting the incorporation of fluoride in the tooth structure also require further investigation. It is necessary to determine the precise crystal structure of dental hard tissues, the process by which they become mineralized, and their chemical interaction with body fluids. New and expanded programs will thus emphasize basic research on the molecular structure of these tissues and on their mineral prototypes which occur elsewhere in nature or can be synthesized in the laboratory. Greater emphasis will also be placed on the role of the fluoride ion in the general metabolic sense, and particularly with regard to its effects on bone metabolism.

Additional information is required to explain the basic biochemical and physiological properties which characterize the types of bacteria associated with caries in crevices, on smooth surfaces, and on root surfaces of the teeth. The finding that caries-conducive streptococci can colonize on the teeth in adherent deposits (plaques) has led to studies of the interaction betwen specific microorganisms, different carbohydrates (sugars and starches) and the chemical nature of the tooth surface. Rampant decay in animals can be induced by feeding a diet containing sucrose and by inoculating specific streptococci isolated from humans or animals. When this occurs the microorganisms involved produce not only acid but also insoluble polysaccharide gums, which appear to be dextrans. Current findings suggest that therapeutic benefit might be attained by finding substances which will solubilize the polysaccharide component in plaque and, if possible, kill the bacteria themselves.

Periodontal Disease and Soft Tissue Studies

A knowledge of the normal structure and function of the periodontal tissues is a prerequisite to understanding the nature of periodontal disease. During 1967, studies in this area will be expanded with special emphasis on the biochemistry of collagen. The breakdown of this protein is a major factor in the pathology of periodontal disease. Additional study of the molecular structure of collagen and of enzymes which cause its degradation will be encouraged.

Since periodontal disease, similar to that in humans, can be produced by a specific bacterium in animals, the search to identify other causative organisms will be intensified during 1967 and 1968. Support will be given to studies of metabolic functions and products of such organisms. Research into the nutritional and hormonal status of host tissues, inadequate oral hygiene, tartar, impacted food, trauma from malposed teeth, and fluoride ingestion will be encouraged.

Calculus, a concretion that forms on the surface of teeth, is considered to be one of the major causes of periodontal disease. Studies of factors which are believed to contribute to the formation of calculus, such as bacteria, salivary composition, and diet, will be supported. It is anticipated that these investigations will lead to the development of chemotherapeutic methods to prevent calculus formation.

The immunologic aspect of periodontal disease is an area requiring a great deal of attention. Current explorations suggest that, in some forms of periodontal disease, one or more antigens in bacterial cells cause an allergic inflammation of the gingival tissues. Other evidence suggests that the body may have a natural immunologic defense against certain oral bacteria associated with periodontal disease. Research will be initiated in this area with the ultimate goal of developing immunizing agents to suppress or destroy bacteria or bacterial products associated with periodontal disease. At the same time, histopathological studies will be further expanded to clarify the relation between gingival inflammation and collagen destruction and bone resorption, in the hope of eventual control of this disease.

Oral and Dental Infections and Conditions

Oral ulcerations occur in well over half of the population and range in severity from an occasional sore to almost constant outbreaks of painful blisters. The principal types of oral ulcerations, which have the common characteristic of recurring at irregular intervals during a person's life, are herpes simplex (fever blisters or cold sores) and aphthous stomatitis (canker sores).

During 1967 and 1968, studies will be initiated to: 1) elucidate the tissue alteration and pathogenesis of the various disease conditions; 2) clarify the histological characteristics of each type of lesion; and 3) develop methods of improving diagnostic technics for these diseases.

Oral Neoplasia

Studies during 1967 and 1968 will be expanded to obtain more definitive information on the nature of tissue changes in leukoplakia and to determine the conditions under which these lesions become malignant. The physiology of normal and abnormal reactions of oral epithelium will also be subjected to extensive microscopic and chemical investigations to provide baseline data for studies of specific neoplastic conditions. Special attention will be focused on the maturation and keratinization of the oral mucosa. Studies of patients with oral lesions considered to be precancerous will be initiated. Technics to improve diagnostic procedures will receive a high priority. Projects to develop therapeutic and prophylactic measures and to determine specific etiologies will be started. In addition, epidemiological investigations are planned to determine the possible role of environmental, nutritional, and genetic factors in the etiology of oral cancer.

Oral Physiology and Endocrinology

In the study of oral physiology and endocrinology, major emphasis will be given to the largely neglected area of salivary glands. During 1967 and 1968, current studies will be expanded to: 1) further investigate structure of the salivary glands; 2) clarify the metabolism of proteins by salivary glands, and determine the sites of transfer of amino acids and their metabolites into saliva; and 3) define the role of the autonomic nervous system in the maintenance of normal structure and function. This research should help delineate the mechanism of secretion of the organic compounds found in saliva and clarify the biological significance of certain secretory components in oral disease.

Normal and Abnormal Growth and Development Including Congenital (Genetic) and Acquired Diseases and Anomalies

The evaluation and refinement of surgical and rehabilitative treatments for the cleft palate child is to be continued during 1968. Studies of psychosocial factors which affect the adjustment of the cleft palate individual and his family to society will be initiated as corollaries to these studies.

New and expanded studies of the causes of the cleft syndromes to clarify genetic and developmental factors are to be emphasized. It is proposed that two centers for multidisciplinary studies into the etiology of clefts be started during 1968. The development of interceptive and corrective treatment procedures for malocclusion will be initiated. 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.

Materials Science

Specific attention will be directed to the development of an adhesive filling material that will bond chemically to the surface 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.

Greater 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 subhuman primates in the same functional capacity as are natural teeth. It is anticipated that clinical trials with human subjects will be conducted in the early future.

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. A beginning has been made in such areas as the development of adhesive dental restorative materials. An important need is the broader application of biomedical engineering research, specifically the advances made possible by space technology.

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 upon developing prostheses (replacement parts) which are more functional and which better meet aesthetic requirements. Studies which characterize the physical, chemical, toxicological, and aesthetic properties of materials for maxillofacial prosthesis will be expanded, and clinical evaluations will be made as new materials become available. One new aspect of this research will focus on polymer degradation due to mechanical stress, chemical absorption, surface defects, and ultra-violet light exposure. Materials and fabrication methods will be altered to eliminate or circumvent failure of the restoration.

Dental Research Institutes (Centers)

A beginning has been made in establishing several dental research institutes as centers of excellence in the sciences related to oral health.

Thus far, in 1967, one application has been approved and funded for the planning of such an institute at the University of Washington in Seattle, and four others are being negotiated for similar planning or developmental phases of research institute support. We view these centers as bringing to bear on oral health problems not only the traditional healing arts but also the broader biological sciences, the behavioral and social sciences, and the engineering and other psysicochemical sciences. Their broad academic settings also provide unique environments for training researchers and academicians.

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	212	$7,449,000	220	$7,737,000	+8	+$288,000
2. Competing projects	91	3,156,000	91	3,436,000	0	+280,000
3. Subtotal, regular program	303	10,605,000	311	11,173,000	+8	+568,000
4. General research support	--------	1,079,000	--------	1,294,000	--------	+215,000
5. Scientific evaluation	--------	42,000	--------	42,000	--------	0
6. Categorical clinical research centers	--------	400,000	--------	400,000	--------	0
7. Dental research institutes	--------	3,000,000	--------	3,000,000	--------	0
8. Total research grants	303	15,126,000	311	15,909,000	+8	+783,000

Research grants program analysis

	1967 estimate	1968 estimate	Increase or decrease
Fields:			
Dental caries and hard tissue studies	$3,235,000	$3,353,000	+$118,000
Periodontal diseases and soft tissue studies	1,984,000	2,034,000	+50,000
Oral and dental infections and conditions	69,000	119,000	+50,000
Oral neoplasia	142,000	242,000	+100,000
Normal and abnormal growth and development including congenital (genetic) and acquired diseases and anomalies	3,157,000	3,207,000	+50,000
Oral physiology and endocrinology	569,000	619,000	+50,000
Materials science	1,449,000	1,599,000	+150,000
Subtotal, regular program	10,605,000	11,173,000	+568,000
General research support grants	1,079,000	1,294,000	+215,000
Scientific evaluation and planning	42,000	42,000	0
Categorical clinical research centers	400,000	400,000	0
Dental research institutes	3,000,000	3,000,000	0
Total research grants	15,126,000	15,909,000	+783,000

Fellowships

	1967 estimate	1968 estimate	Increase or decrease
Total fellowships	$1,691,000	$1,971,000	+$280,000

PROGRAM PLANS IN 1967 AND 1968

The fellowship program complements the training grant program by providing training opportunities in qualified departments in colleges and universities which do not have training grant support. A wider selection of training disciplines and locations is thereby afforded.

Support for advanced research training not commonly available under the training grant program also is provided under the special fellowship and research career development award portions of the fellowship program.

An increase of $280,000 is requested, of which approximately $83,000 will be used to support 10 additional regular fellowships, and $197,000 will be used to support 15 research career development awards. Special emphasis will be placed on such areas as: the etiology and epidemiology of periodontal disease, diseases of the salivary glands and the role of their secretions in oral health, psychological factors underlying dental problems, and cleft palate and orthodontic problems.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	79	$1,216,000	88	$1,355,000	+9	+$139,000
(b) Competing	5	80,000	10	120,000	+5	+40,000
2. Supplementals	(5)	6,000	(5)	6,000	(0)	0
3. New awards	51	389,000	62	490,000	+11	+101,000
4. Total fellowships	135	1,691,000	160	1,971,000	+25	+280,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Predoctoral	10	$57,000	15	$93,000	+5	+$36,000
2. Postdoctoral	63	522,000	63	522,000	0	0
3. Special	15	133,000	20	180,000	+5	+47,000
4. Research career:						
(a) Career	4	112,000	4	112,000	0	0
(b) Development awards	43	867,000	58	1,064,000	+15	+197,000
5. Total fellowships	135	1,691,000	160	1,971,000	+25	+280,000

TRAINING GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Total training grants	$5,398,000	$5,469,000	+$71,000

PROGRAM PLANS FOR 1967 AND 1968

The graduate training grant program continues to provide the major source of support for individuals training for careers in dental research and teaching.

Recent developments have emphasized the importance of microbiological research to the ultimate alleviation of the dental caries problem. The striking geographic differences in the occurrence of this disease underline the importance of epidemiologic studies to determine the causes of these variations. Accordingly, it is proposed to initiate training programs to provide additional scientists qualified in these two research fields.

Research on the etiology and treatment of malocclusion, a condition which affects a high proportion of children, is primarily concerned with facial growth and development. In order to expand this area of research, the Institute plans additional programs which will train individuals with the necessary clinical skills in the disciplines associated with development; e.g. embryology, anthropology, and genetics.

More information is needed concerning the patterns of initiation and progression of periodontal disease in various population groups on a long-term basis. It is proposed, therefore, to augment the Institute's training efforts to provide scientists with skills in such fields as nutrition, genetics, the behavioral and social sciences, and epidemiology and biometry.

There is an urgent need for increased research in dental biomaterials such as those employed in the restoration of lost tooth structure and in the correction of facial disfigurement resulting from congenital malformations and from oral and facial cancer. To increase the scientific capabilities devoted to these important objectives, additional training opportunities will be provided in disciplines such as polymer chemistry, metallurgy, ceramics, solid state physics, and special fields of engineering.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	82	$3,843,000	75	$3,525,000	−7	−$318,000
(b) Competing	14	888,000	32	1,572,000	+18	+684,000
2. Supplementals	(10)	176,000	(10)	180,000	(0)	+4,000
3. New grants	13	466,000	4	167,000	−9	−299,000
4. Scientific evaluation	(1)	25,000	(1)	25,000	(0)	0
5. Total training grants	109	5,398,000	111	5,469,000	+2	+71,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Graduate training grants:						
1. Basic sciences	86	$4,268,000	88	$4,339,000	+2	+$71,000
2. Clinical sciences	23	1,105,000	23	1,105,000	0	0
3. Scientific evaluation	(1)	25,000	(1)	25,000	0	0
4. Total training grants	109	5,398,000	111	5,469,000	+2	+71,000

LABORATORY AND CLINICAL RESEARCH

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	232	$2,177,800	237	$2,324,900	+6	+$147,100
Other expenses	-------	1,862,200	-------	2,273,100	-------	+410,900
Total	232	4,040,000	237	4,598,000	+6	+558,000

INTRODUCTION

The ultimate goal of the Institute continues to be that of reducing the prevalence of oral-facial malfunction, irrespective of whether it expresses itself in the form of dental caries, periodontal disease, oral cancer or of anomalous oro-facial development. This essential end point can be attained only upon the accumulation and application of a substantially larger body of information regarding causal factors than is presently at hand.

Implementation of the Institute's mission is being served simultaneously by a tripartite research approach involving: 1) basic laboratory investigations of relevance to oro-facial disease; 2) clinical and applied investigations relating to specific disease entities; and 3) epidemiological and field studies, largely directed toward determining feasibility and efficacy of concepts and/or technics generated by the laboratory and clinical endeavors to alleviate oro-facial disease.

PROGRAM PLANS IN 1967 AND 1968

Dental Caries

Basic laboratory studies in the Institute have already demonstrated that a strain of streptococcus is strongly implicated in the genesis of dental decay in laboratory animals. Clinical investigation of so-called "caries susceptible" humans has also revealed that similar bacteria may be isolated from the oral cavity. The recent development of technics which permit isolation, cultivation, and preservation of the human bacterial sample now provides the means whereby additional laboratory and clinical studies may be undertaken, with particular reference to characterizing the organism in terms of its metabolic requirements, and ultimately in terms of its vulnerability to specific antibiotic or related prophylactic measures.

Moreover, these technical developments now permit additional epidemiological study directed toward elucidation of the factors which may influence the prevalence and virulence of this and related organisms in large patient populations.

Notwithstanding the probable role of oral microorganisms in the genesis of dental decay, it is now well established that the addition of fluoride, either by direct (topical) application to the teeth, or by its inclusion in the drinking water, can alter the dental enamel in such a way as to make it less susceptible to decay. The Institute takes pride in its past role in the development of this significant contribution to the nation's health, and maintains a strong interest in gathering further knowledge concerning the as yet incompletely documented potential of this unique substance. Consequently, basic laboratory investigations on the mechanism by which the fluoride ion alters enamel structure, especially with respect to its possible use in reversing the early caries process, are con-

tinuing. Similarly, considerable effort is being expended in the area of field testing, with emphasis on the epidemiological efficacy of newer methods of topical application of fluoride to the teeth of young people.

Peridontal Disease

As in the case of dental caries, laboratory animal experiments have now revealed that a filamentous microorganism, previously isolated from a diseased periodontium, elicits a response in the host which is clinically similar to human periodontitis. The significance of this finding to the human condition, however, requires much additional study, particularly in terms of characterization of the organism, as well as of its incidence in the normal and diseased human oral cavity.

Laboratory and clinical studies, which emphasize our need to know much more regarding the chemical and metabolic properties of the oral connective tissues, continue to be an integral facet of the Institute's total research endeavor. These studies are designed to determine the nature of the factors which normally influence the synthesis and breakdown of the major structural constituents of connective tissue, proteins, collagen, and elastin, the integrity of which is seriously compromised in periodontal disease. At the clinical level, too, greater emphasis is to be given to the possible role of systemic factors, including nutrition, drugs and hormones, systemic diseases, etc., in determining the susceptibility to and severity of periodonitis. Further clinical and epidemiological effort will be applied to the performance of the relationship between the various clinical signs of periodontal disease and its pattern of development, with the ultimate goal of determining rational methods of clinical therapy, which up to this point in time have been largely empirical.

Oral Cancer

Certain white patches of tissue on the lip, tongue or mouth lining, generally categorized as leukoplakia, are thought to be precancerous. Current research will be expanded to seek more definitive information on the nature of tissue changes in leukoplakia, utilizing biochemical and ultrastructural methods in the laboratory. In addition, clinical and epidemiological investigations of the prevalence and natural history of leukoplakia, with particular reference to environmental factors which may increase the probability of malignant transformation in the lesion, will form an integral part of the total Institute effort with regard to oral cancer.

Growth and Development

Oral clefts, which are among the most common oral-facial defects at birth, result from a failure of the right and left segments forming the lip and the roof of the mouth to unite along a line beginning at the lip and extending through the hard and soft palate. Thus, there is no intact partition between the oral and nasal cavities. Dental abnormalities, such as malformed teeth and arches, are characteristic of this condition. Total collapse of the maxillary arch is common with attendant orthodontic, prosthodontic, and orthopedic problems. Impairment of speech, breathing, and swallowing, and increased susceptibility to upper respiratory infections frequently result.

Successful rehabilitation of the cleft palate child involves the coordinated efforts of many specialists, including orthodontists, prosthodontists, plastic and oral surgeons, otolaryngologists, phychologists, speech therapists, and social workers. It is estimated that the total direct costs for treatment of a single case, covering the period from birth to sixteen years of age, run from $5,000 to $10,000, with variations depending upon the region of the United States in which treatment is given.

In order to clarify the role of genetics and environmental factors in the incidence of cleft palate, detailed genetic, social, medical, and reproductive histories of 100 Pennsylvania families with oral clefts are being obtained. Information emerging from this investigation, as well as currently supported studies on twins, will be useful for both predictive and counseling purposes.

Included in this net increase is $18,000 for mandatory items such as annualization of positions new in 1967, offset by $7,000 for one less day of pay in 1968. There is also an increase of $159,000 for centrally furnished services from the National Institutes of Health Management fund.

Collaborative Research and Development

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	3	$34,400	4	$47,200	+1	+$12,800
Other expenses		676,600		812,800		+136,200
Total	3	711,000	4	860,000	+1	+149,000

PROGRAM PLANS FOR 1967 AND 1968

These funds will be utilized primarily in research and development of a satisfactory adhesive dental restorative material in collaboration with industrial laboratories, universities, and research organizations.

Collaborative research activity will further emphasize research on implantation and transplantation technics, including basic studies related to tissue-implant/transplant reactions.

In addition it is planned to study the natural cements produced by barnacles, and possibly other aquatic animals or plants, which naturally withstand temperature changes, pressures, reactive chemicals, and still adhere for years to anything solid in an aqueous environment. Moreover, these cements attract mineral salts from water to increase the area of attachment as time goes on.

Included in this net increase is $2,000 for centrally furnished services from the National Institutes of Health Management Fund.

Biometry, Epidemiology and Field Studies

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	23	$254,400	23	$260,400	0	+$6,000
Other expenses		172,600		174,600		+2,000
Total	23	427,000	23	435,000	0	+8,000

PROGRAM PLANS IN 1967 AND 1968

Biometric and epidemiological field studies require the application of dental and medical knowledge to human population studies and require original research in mathematical statistics, demography and general methodology for data handling, reduction and analysis.

Epidemiologic studies are being conducted to further clarify the interactions of factors responsible for tooth decay; that is, to determine whether decay producing organisms are natural inhabitants of the oral cavity or whether organisms must be transmitted to the oral cavity before the disease can be established. Another approach is an investigation of the geographic pathology of caries. In this connection, it is planned to conduct field studies in various areas of the Middle East and Africa, such as Ethiopia, where one of the lowest frequencies of tooth decay in the world is found, before encroachments of civilization change this pattern.

Similarly invaluable knowledge can be gained about periodontal disease and growth and development from studies of groups of individuals still living under relatively primitive conditions.

The genetic factor in studies of a broad segment of general population is very much in evidence. For the first time, it has been demonstrated in clinical surveys that heredity is a factor in dental caries.

Included in this net increase is $2,000 for centrally furnished services from the National Institutes of Health Management Fund.

Review and Approval of Grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	40	$378,000	40	$388,000	0	+$10,000
Other expenses		241,000		274,000		+33,000
Total	40	619,000	40	662,000	0	+43,000

The funds for this activity support the Institute's scientific, managerial, and clerical staff, the National Advisory Dental Research Council and various other subcommittees in the direction and coordination of the grants program. The Council and staff are responsible for stimulating research interest in areas of critical need, reviewing, analyzing, and processing of the research and training grant applications, as well as maintaining a continuing review of ongoing research and training programs.

Included in this net increase is $21,000 for centrally furnished services from the National Institutes of Health Management Fund, offset by $1,000 for one less day of pay in 1968.

Program Direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	26	$241,400	26	$248,400	0	+$7,000
Other expenses		150,600		154,600		+4,000
Total	26	392,000	26	403,000	0	+11,000

This activity supports the overall administration, coordination, and direction of the varied programs and activities of the Institute. The Director and his immediate staff are responsible for the overall program development and review of new areas of focus and interest, as well as introducing new knowledge into current operating programs.

Included in this net increase is $4,000 for centrally furnished services from the National Institutes of Health Management Fund.

New positions requested, fiscal year 1968

	Grade	Annual salary
Laboratory and clinical research:		
Microbiologist	GS-9	$7,696
Research technician	GS-7	6,451
Dental directors (2)	C.O.	33,838
Senior dental surgeons (2)	C.O.	24,424
Total (6)		72,409
Collaborative research and development: Scientist administrator	GS-13	12,873
Total new positions, all activities (7)		85,282

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. BENJAMIN T. BURTON, ASSOCIATE DIRECTOR FOR PROGRAM ANALYSIS AND SCIENTIFIC COMMUNICATION, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
W. GILBERT BAYLIS, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	5,745	6,437	6,701
11.3	Positions other than permanent	165	190	190
11.5	Other personnel compensation	42	50	50
	Total personnel compensation	5,953	6,677	6,941
12.0	Personnel benefits	610	688	708
21.0	Travel and transportation of persons	226	265	330
22.0	Transportation of things	49	60	60
23.0	Rent, communications, and utilities	154	158	175
24.0	Printing and reproduction	32	55	60
25.1	Other services	849	886	1,114
	Project contracts	2,349	5,020	7,650
25.3	Payment to: "National Institutes of Health management fund"	5,709	5,766	6,448
26.0	Supplies and materials	1,038	1,105	1,115
31.0	Equipment	622	694	770
41.0	Grants, subsidies, and contributions	103,902	111,615	118,601
	Subtotal	121,493	132,989	143,972
95.0	Quarters and subsistence charges	−18	−18	−18
99.0	Total obligations	121,475	132,971	143,954

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	710	683	701
Full-time equivalent of other positions	17	18	18
Average number of all employees	616	670	711
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	84,176	90,629	96,304
(b) Fellowships	5,522	6,129	6,591
(c) Training	14,204	14,857	15,706
Total grants	103,902	111,615	118,601
2. Direct operations:			
(a) Laboratory and clinical research	12,142	13,248	14,333
(b) Collaborative research and development	794	5,124	7,736
(c) Biometry, epidemiology, and field studies	576	730	751
(d) Review and approval of grants	1,869	1,924	2,157
(e) Program direction	308	330	376
Total direct operations	15,689	21,356	25,353
Total program costs funded [1]	119,591	132,971	143,954
Change in selected resources [2]	1,884		
10 Total obligations	121,475	132,971	143,954
Financing:			
16 Comparative transfer to other accounts	144	980	
25 Unobligated balance lapsing	1,581	1,724	
New obligational authority	123,200	135,675	143,954
New obligational authority:			
40 Appropriation	123,203	135,687	143,954
41 Transfer to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−3		
"Operating expenses, Public Buildings Services," General Services Administration (80 Stat. 674)		−12	
43 Appropriation (adjusted)	123,200	135,675	143,954
Relation of obligations to expenditures:			
10 Total obligations	121,475	132,971	143,954
70 Receipts and other offsets (items 11-17)	144	980	
71 Obligations affecting expenditures	121,619	133,951	143,954
72 Obligated balance, start of year	54,479	76,065	92,811
74 Obligated balance, end of year	−76,065	−92,811	−117,306
77 Adjustments in expired accounts	−2,138		
90 Expenditures	97,896	117,205	119,459

[1] Includes capital outlay as follows: 1966, $574,000; 1967, $694,000; 1968, $770,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $859,000 (1966 adjustments, −$8,000); 1966, $2,735,000; 1967, $2,735,000; 1968, $2,735,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. We have before us this afternoon Dr. G. Donald Whedon, Director of the National Institute of Arthritis and Metabolic Diseases.

There is a biographical sketch of Dr. Whedon which we shall insert at this point in the record.

(The biographical sketch follows:)

Name: Dr. G. Donald Whedon.
Position: Director, National Institute of Arthritis and Metabolic Diseases (NIAMD).
Birthplace and date: Geneva, New York, July 4, 1915.
Education: A.B., 1936, Hobart College; M.D., 1941, University of Rochester School of Medicine.

Experience: Director, NIAMD, 1962–present; Assistant Director, NIAMD, 1956–1962; Chief, Metabolic Diseases Branch, NIAMD, NIH, 1952–1965; Physician, Outpatient Dept., New York Hospital, 1947–1952; Assistant Physician, Outpatient Dept., New York Hospital, 1944–1947; Assistant Professor of Medicine, Cornell University Medical College, 1950–1952; Instructor of Medicine, Cornell University Medical College, 1944–1950; Assistant in Medicine, University of Rochester School of Medicine, and Assistant Resident Physician in Medicine, Strong Memorial Hospital, 1942–1944; Interne in Medicine, Mary Imogene Bassett Hospital, Cooperstown, New York, 1941–1942.

Association memberships: Association of American Physicians; The Endocrine Society (Postgraduate Committee, 1962–1965); 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.

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, 1959–1961; Subcommittee on Calcium, Committee on Dietary Allowances, Food and Nutrition Board, Journal of Clinical Endocrinology and Metabolism, 1960–present; NIAMD representative, NIH Task Force—Off-site research installations, 1960; Consultant to Space Medicine Division, Office of Manned Space Flight, NASA, Nov. 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 matabolic and physiological studies of convalescence, immobilization, paralytic poliomyelitis, diseases of bone particularly including osteoporosis, human energy metabolism and space medicine.

Mr. FLOOD. I see, Doctor, you have a statement. I suppose you would like to proceed?

Dr. WHEDON. I would, if I may.

Mr. FLOOD. Please proceed.

GENERAL STATEMENT

Dr. WHEDON. Mr. Chairman and members of the committee, I am grateful once again for the opportunity to report to you on the programs of the National Institute of Arthritis and Metabolic Diseases and to testify to the progress and needs of these programs for the next fiscal year.

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 history of medicine and of biomedical research and our own experience has taught us that major breakthroughs in the treatment and control of a disease usually depend on pertinent advances in fundamental knowledge applicable to the disorder, and that pursuit of a disease problem along purely clinical or applied lines sooner or later reaches a point of rapidly decreasing return because of serious limitations in fundamental knowledge and techniques. 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. In my testimony today I would like to touch upon activities and achievements along all of these lines, none of which can be looked upon as distinct and exclusive methods of approach to the solution of the health problems of the Nation.

Although many significant contributions have been made by Institute and Institute-supported scientists, in this brief report I can mention only a few examples of the heartening progress made since last year. With the permission of this committee, I would like to submit separate, more detailed special reports dealing with specific achievements and progress brought about by Institute scientists or grantees in the areas of arthritis and rheumatic diseases, diabetes, gastrointestinal diseases, and cystic fibrosis. I would also like to append a comprehensive progress report on research in the field of kidney diseases for which the prime responsibility lies with this Institute, but in which other specialized aspects are pursued through coordinated efforts in two other Institutes as well.

ARTHRITIS

The main thrust of present studies in arthritis is directed against the most crippling of the arthritic disorders, rheumatoid arthritis, where new etiologic possibilities have been uncovered recently. Two types of microorganisms that have been implicated in recent reports in joint diseases in animals are now being studied in relation to the rheumatic diseases. The possible role of mycoplasmas (microorganisms with characteristics between bacteria and viruses) in causing rheumatoid arthritis is now being investigated, as well as the possible causative role of viruses belonging to the genus *Bedsonia*. This last year, investigators have produced arthritis in monkeys by injecting them with *Bedsonia* organisms isolated from human patients with Reiter's syndrome, a disease closely related to rheumatoid arthritis. Another group of investigators has reported a study which offers hope for an effective form of therapy in rheumatoid arthritis and, possibly, in other diseases caused by faulty immune mechanisms (autoimmunity). They produced adjuvant arthritis (an experimentally induced form of arthritis affecting many joints and exhibiting a true, but transitory, immunological reaction) in rats by injecting them with Freund's adjuvant, a material used in many immunity studies. Treatment of these rats with rabbit antilymphocyte serum successfully suppressed

the usual arthritis reactions in these rats; in contrast, untreated control animals all developed marked polyarthritis. This important research lead is being followed up with additional studies to determine its possible applicability to treatment of human arthritis.

Based on their studies on osteoarthritis (degenerative arthritis), investigators supported by this Institute have reported on the likely clinical value of a special cartilage-bone marrow extract preparation in the treatment of this disorder. At the same time, other investigators have reported favorable results obtained in the treatment of rheumatoid arthritis with cyclophosphamide, a cytotoxic drug originally develop as an anticancer agent. Both studies represent early work on potentially important advances and thus warrant further investigation and continued clinical trials in order to elucidate the respective mechanisms of action, precise limits of effectiveness of the treatment, and the extent of side effects during prolonged treatment, if any.

Last year I reported to the committee encouraging experiments with a new drug, allopurinol, which is capable of depressing uric acid formation in patients with gout. In this inherited metabolic disorder, uric acid crystals are deposited in and around the joints (and in other tissues), resulting in inflammation, severe pain, and eventual destruction of normal joint structure. In severe cases, permanent crippling or severe kidney damage, or both, may result. Continued experience with the new drug has, indeed, justified our optimism as to its efficacy in the treatment of this disease. At the present time, gout can be the best controlled of all the arthritic diseases. Current treatment, much of which has evolved under Institute sponsorship, aims at controlling excess uric acid accumulation in the body and at preventing or relieving the recurrent painful attacks. Potent drugs developed during the last few years can now be used to suppress abnormal uric acid synthesis or to stimulate its excretion via the urine, thus preventing a buildup of harmful crystal deposits in the joints, in the urinary tract, and in other tissues. At this point our future research emphasis will be on development of methods of early diagnosis of this inherited metabolic disorder to permit prompt treatment and consequent avoidance of joint damage and kidney complications.

DIABETES

In diabetes research, we have passed through a recent phase in which significant advances have been made in therapy, notably development of the oral drugs for better blood sugar control of the older diabetic patient. Now we are beginning to enter a phase in which we are approaching more fundamental aspects, specific pathological tissue and molecular changes which should lead us closer to the cause of the disease.

In previous testimony before this committee I have distinguished between two clinical types of diabetes—juvenile diabetes ("brittle" diabetes) and maturity-onset diabetes ("stable" diabetes)—which have different prognoses, somewhat different treatment, and related, but possibly dissimilar, causative mechanisms. The onset of the "brittle" type of diabetes frequently occurs during childhood or the teens. Although the great majority of such patients can be maintained with regular insulin injections, life expectancy of the patient with this type of diabetes is considerably shortened.

It has recently been proposed that inheritance and development of diabetes may be related to a natural insulin made by the patient's pancreas with an abnormal molecular structure. This concept has gained support during the past year from the work of an Institute-supported investigator who has shown that insulin isolated from the blood of diabetic children is resistant to destruction by a specific enzyme capable of degrading insulin from normal individuals. This resistance of juvenile diabetes insulin to the enzyme may be the result of a structural abnormality in this insulin molecule. This finding suggests that there is a genetically determined difference in the insulin in juvenile diabetes which contributes significantly to the underlying biochemical disorders of the disease.

In previous testimony I have mentioned the finding that the Egyptian sand rat has been discovered to be a suitable experimental animal model for diabetes resembling the human maturity-onset type of the disorder. This development of the recent past is expected to aid greatly in diabetes-related research by providing a system for observing more closely the altered body chemistry of diabetes and a means of testing the effects thereon of treatment possibilities. I am now pleased to follow up my previous testimony with the report from Institute-supported investigators who have recently described a metabolic disorder closely resembling human juvenile diabetes which has appeared as a new genetic mutation in inbred mice. Because the disease is readily reproducible, the new strain of mice will provide a much needed experimental animal model for research on juvenile diabetes.

It has been generally accepted that abnormal carbohydrate metabolism is the initial manifestation of clinical diabetes and that the small blood vessel abnormalities of the disorder which are responsible for some of its severe complications, develop only subsequently, as the disease progresses. Institute grantees have recently reported a very significant finding in prediabetic individuals—persons having two diabetic parents and genetically destined to develop diabetes sometime during their lives, but who do not display as yet any chemical aberrations of the disease. These investigators were able to demonstrate that significant small blood vessel disease in muscles, expressed in the form of marked thickening of the basement membrane of capillaries, which is characteristic of overt diabetes, appears in at least 50 percent of genetically prediabetic subjects prior to the onset of carbohydrate abnormalities and in practically all diabetic patients thereafter. These findings suggest that small blood vessel basement membrane thickening may represent the primary lesion of diabetes, followed only secondarily by carbohydrate derangements. The significance of this observation is that diabetes investigators are now afforded a new angle of attack, a direction for research efforts which may be much more fruitful in determining the fundamental cause of diabetes than previous studies directed mainly toward the abnormality in carbohydrate metabolism.

GASTROENTEROLOGY

Institute acceleration in studies of peptic ucler is beginning to bear significant results against this disorder which strikes about 10 percent of all adults in the United States at some time or other in their lives. I am pleased to report that the studies of one Institute

grantee have now demonstrated the efficacy of a new compound, amylopectin sulfate, in the treatment of patients with chronic duodenal ulcer disease and in the prevention of recurrences of such ulcers. This substance does not appear to exert an antacid or anticholinergic action in the manner of currently used antipeptic ulcer agents but, according to the investigator, exhibits a direct inhibitory effect on secretion of acid and pepsin by the stomach mucosa.

Other achievements in the area of gastroenterology include a new treatment for malabsorption in intestional scleroderma, a new diagnostic technique to detect patients with ulcerogenic tumors of the pancreas, the successful use of exchange transfusions in moribund patients with hepatitis, and many others. The Institute intends to increase its efforts to develop new methods for overcoming acute liver failure, a condition heretofore not amenable to effective therapy. Experience gained in the Institute's artificial kidney program is expected to find application in evolving methodology for management of liver failure.

KIDNEY DISEASE

Although this report by necessity is brief, I must mention progress in artificial kidney development in which the Institute has launched an energetic planned program of research and development and in which this committee has shown particular interest. Here a group of Institute-supported investigators have developed a new artificial kidney which is considerably smaller and more efficient than existing types. The new device costs half as much as the conventionally used Kiil dialyzer, can be assembled in 10 minutes and can be sterilized in an autoclave. Being compact, it has decreased very considerably the presently high blood priming requirement and the need for compensatory blood transfusions. This new artificial kidney can cleanse a patient's blood in 8 to 10 hours, compared to the 12 to 14 hours needed with the Kiil unit; thus, the bed capacity of artifical kidney treatment centers can be increased considerably with the aid of the new device. At the present time a series of these new artificial kidneys is being produced for extensive testing under routine operating conditions. By no means is this a final solution to the problem, but it is a definite forward step toward greater efficiency and reduced cost in the artificial kidney approach to management of chronic kidney disease.

The Institute's new artificial kidney program has initiated a large series of research and development contracts aimed at reduction of cost and improvement of existing dialysis ("blood cleansing") methods and equipment or at completely new approaches to artificial replacement of impaired kidney function. These projects involve development of improved blood cannulas (the most significant bottleneck in current dialysis), development and evaluation of new plastic surfaces for artificial kidneys, cannulas, and membranes which will not induce blood coagulation, improved dialysis membranes, development of new concepts in artificial kidney design such as "diafiltration" (a manmade imitation of the function of the natural kidney) and "hollow fiber" kidneys, evaluation and development of a special diet which could delay for substantial periods the need for intensive dialysis, or for use in maintenance of uremic patients for whom chronic dialysis is deemed not feasible or is unobtainable, and many

other projects related to improved and less expensive dialysis methodology or apparatus. Concurrently, through related grant-supported studies, the Institute endeavors to learn more about the biochemical and physiological characteristics of chronic kidney failure, a requisite for a rational design of more efficient artificial kidneys, and for better rehabilitation of patients maintained through dialysis. In additon, considerable efforts in improvement of techniques in kidney transplantation are being supported by the Institute through its grants program.

In conclusion, many other achievements of the yast year could be cited in endocrinology and endocrine disorders, in hematology, and in the other areas of responsibility of the National Institute of Arthritis and Metabolic Diseases. I shall be glad to answer any question on these areas.

During the coming year the Institute intends to devote increasing attention to the planning of its research activities and support, taking into account emerging new laboratory and clinical developments, the state of the art in the various disease areas, the possibilities for prompt application of new findings to patient care, and the possible need for special development programs in situations where the planned exploitation of new knowledge appears particularly promising. I am looking forward to another year in which we shall continue the Institute's sound and productive pursuits in health research and research training, and I wish to thank and commend this committee for enabling us to continue our unrelenting effort toward better health for our citizens.

Mr. Chairman, I am submitting a request for $143,954,000 as compared with the operating level of $132,971,000 for 1967. The proposed increase for fiscal year 1968 will provide for an estimated additional 46 extramural research projects, for an orderly continuation of research training and fellowships and of our sound direct research efforts in Bethesda, and for continued acceleration of our artificial kidney program.

(The special reports referred to above follow:)

SPECIAL REPORT—GASTROENTEROLOGY

The field of gastroenterology continues to prove one of the more difficult and fascinating for biomedical research investigators. Due to the nature and diversity of gastroenterological diseases and disorders, research progress is achieved only after the most intensive, deliberate and time-consuming laboratory and clinical trials and experiments. Responsibility for the support of research in this area is a primary function of the National Institute of Arthritis and Metabolic Diseases (NIAMD).

Gastroenterology is not only vast from the standpoint of the number of individuals afflicted by disorders of the intestinal tract but also because of the extensive number of diseases it encompasses. Included are not only the better known disorders such as peptic ulcer, ileitis, and ulcerative colitis, but also numerous diseases of the intestine and its appendages about which much remains to be learned, such as diseases of the liver, gallbladder and pancreas.

Figures published last May by the Public Health Service in a study entitled "Estimating the Cost of Illness" (Health Economic Series No. 6) present impressive statistics on the direct expenses and indirect costs of sickness in the Nation. According to the study, which analyzes health, medical and related costs, the annual direct and indirect costs of illness, disability and death in the U.S. in 1963 exceeded $58 billion, including $34.3 billion expended for health care, services and supplies, and $23.8 billion in indirect costs. In particular, the study noted

that direct expenditures for diseases of the digestive system in 1963—$4.2 billion or nearly 20% of the total—were higher than the expenditures for any other category of disease. Moreover another $1.3 billion were attributed to diseases of the digestive system in indirect costs.

It is estimated that approximately 14 million Americans, or over seven percent of the entire U.S. population, now have or have had an ulcer of the stomach or duodenum. Each day, according to health statistics, an estimated 4,000 more individuals develop an ulcer, and every year about 10,000 persons die of complications of peptic ulcer. The cost in terms of lost man hours and direct medical expenses due to peptic ulcer alone is estimated at $500 million annually.

The past year has seen several significant and far-reaching research findings in the field of gastroenterology by NIAMD scientists and investigators receiving grant support from the Institute. Foremost among these are improved therapeutic and diagnostic techniques for peptic ulcer, and observations related to problems of milk intolerance, malabsorption, intestinal absorption of calcium, intestinal hemorrhage, morphological changes in the human intestinal mucosa occurring during abdominal X-ray therapy, and ulcerogenic tumors of the pancreas.

Peptic Ulcer

In the search for an antipeptic agent, attention has been drawn to the sulfated polysaccharides because of their interference with peptic digestion. In a series of investigations, an Institute grantee has shown that amylopectin sulfate is an effective antipeptic agent in the treatment of patients with chronic duodenal ulcer disease.

Initially, the effect of a single oral administration of amylopectin sulfate, at five dosage levels, was studied. In a second group of experiments, the effect of repeated administrations of amylopectin sulfate, alone and in combination with propantheline bromide (an anticholinergic drug which inhibits gastric acid and pepsin secretions at their source), on gastric peptic activity was studied. The addition of propantheline bromide was found to enhance the action of amylopectin sulfate. Since the later exerts no antacid or anticholinergic action, the investigator concluded that its inhibitory effect on peptic activity must be a direct one.

Finally, another study was then conducted to determine the long-term effects of amylopectin sulfate, propantheline bromide, and a combination of both, on the prevention of recurrences of peptic ulcer disease. In a double-blind study of 60 patients with chronic duodenal ulcers conducted over a one-year period, it was found that patients responded significantly better on amylopectin sulfate alone, or in combination with propantheline bromide, than they did on propantheline bromide alone or on placebo therapy.

In another investigation, scientists receiving support from the Institute have challenged accepted principles of antacid therapy for duodenal ulcer by showing that antacid compounds have a surprisingly long effect on gastric acidity when given *one hour after a meal.* Current use of antacid drugs in the management of duodenal ulcer, although subject to some controversy, is generally well accepted. The rationale for such therapy, however, is based largely on results of studies in fasting duodenal ulcer patients, which have shown that antacid act for only 20 to 40 minutes (due to rapid gastric emptying), and that doubling the standard dose does not prolong neutralization. The effect of antacids on gastric acidity now has been determined in duodenal ulcer patients following ingestion of a standard meal. Administration of a standard dose of antacid one hour after the meal depressed gastric acidity for at least three hours, while doubling the dose exerted an even greater effect and prolonged the drug's action. These findings suggest that the conveniently accepted antacid studies in *fasting* ulcer patients, and the conventional directions for taking antacid compounds (usually 2 or more hours after meals), should not form the basis for current principles of antacid therapy, and indicate that administration of antacid drugs in usual doses one hour after a meal constitutes rational and effective duodenal ulcer therapy.

Meanwhile, research findings of another Institute grantee indicate that the development of stress ulcers is preceded by gastric hypersecretion resulting from hyperplasia of all gastric mucosal cellular elements. Stress ulcers often occur repidly in the stomach following surgery, physical or emotional trauma, or administration of steroid drugs. While it is known that stimulation of the central parasympathetic nervous system causes hypersecretion of hydrochloric acid and pepsin (both known ulcerogenic factors), the gastric mechanism responsible has

not been elucidated. The Institute grantee, in this study, showed that continuous central parasympathetic stimulation causes marked hyperplasia of all gastric mucosal cellular elements, followed by development of gastric ulcers histologically indistinguishable from those seen in patients with chronic ulcer disease. These findings suggest that formation of stress ulcers is preceded by gastric hypersecretion resulting from gastric mucosal hyperplasia.

Also of considerable interest in the field of peptic ulcer research is the recent finding of another Institute-supported scientist who reported a decline in the rate of recurring ulcers to one-half of one percent when surgery has been done optimally. Just prior to World War II, ulcers recurred in 15 out of every 100 patients treated by surgery. At the turn of the century, the recurrence rate was about 80 percent. Most recurrences are suffered by patients whose original ulcer was of the duodenal variety, which is about ten times more frequent than gastric ulcers. The current favored treatment for duodenal ulcer, the investigator reported, now includes surgical removal of only 30 percent of the stomach. Prior to World War II as much as 70 to 75 percent of the stomach was removed, and this led to a higher percentage of undesirable postsurgical complications than the minimal removal favored at present.

Intolerance to Milk

Last year Institute-supported researchers traced the cause of milk intolerance in certain otherwise normal adults and in patients with inflammatory bowel disease to a deficiency of the intestinal enzyme lactase, which converts lactose or "milk sugar" into glucose and galactose. Evidence also was found that intolerance to milk is a relatively common syndrome in adults. Other Institute grantees now have shown that this syndrome is much more common in the Negro population than in the white, suggesting that intestinal lactase activity levels are genetically controlled. Lactose (milk sugar) tolerance and glucose-galactose tolerance tests were preformed on 40 randomly selected healthy adult male subjects, 20 Negro and 20 white. Small-intestine biopsies were obtained and assayed for lactase and related sugar-splitting enzymes. Nineteen Negro and two white subjects gave histories of milk intolerance with onset during or after adolescence.

Lactose intolerance, as revealed by test and accompanied by abdominal symptoms, occurred in 20 of the 21 milk-intolerant subjects, of whom 18 were Negroes. In milk-tolerant control subjects, lactose tolerance tests were normal and were not accompanied by symptoms. Combined glucose-galactose tolerance tests did not produce symptoms in any subjects. Intestinal lactase deficits as determined by biopsy were observed in 14 of the 20 Negro subjects, but in only one of the 20 white males. This marked racial difference in the prevalence of lactase deficiency suggests a possible genetic etiology for which there is a precedent—previous reports of severe diarrhea in both children and adults due to inherited deficiencies of lactase and related intestinal enzymes. The Institute investigators suggest that environmental or selective factors in Africa may have played a role in establishing and maintaining low lactase levels as an inherited trait. They also suggest that the African ancestors drank very little milk after weaning, resulting in a diminished stimulus to production of lactase.

This study has considerable diagnostic and therapeutic significance, with particular import for Negro patients presenting with a variety of gastrointestinal symptoms, such as diarrhea, nausea, 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.

Since completion of this study, an article from Uganda reported a 72 percent incidence of lactase deficiency in African Negroes, a figure strikingly similar to that reported by the grantees' study in Baltimore. Tribal differences found in the Uganda study provide further evidence of a hereditary basis for lactase deficiency.

New Treatment of Malabsorption in Intestinal Scleroderma

The etiology of malabsorption in patients suffering from intestinal scleroderma (in which the basic changes in the gastrointestinal tract are atrophy and fibrosis of the smooth-muscle coats) has been the subject of considerable debate. Malabsorption in this disease is characterized by abdominal distention and discom-

fort, vomiting and diarrhea. In this study by an Institute grantee, three of four patients with documented malabsorption related to intestinal scleroderma responded dramatically to broad-spectrum antibiotics with remission of their symptoms and improved absorption. The findings suggest the usefulness of this form of treatment and the possible role of bacteria in the pathogenesis of malabsorption in these patients.

Each patient had evidence of disseminated scleroderma for many years prior to onset of intestinal symptoms, and in each, symptoms of esophogeal disease preceded those of intestinal involvement. Malabsorption was proven by sensitive absorption tests. Bacterial proliferation in the upper small intestine was suggested by increased urinary excretion of the tryptophan metabolite, indican (indoxyl sulfate), and was confirmed by culture of aspirated duodenal contents. During prolonged antibiotic therapy, two patients who had been semi-invalids regained 20 and 15 pounds in weight, respectively, and were able to resume normal activity. The only complication of prolonged antibiotic therapy during the study was a single episode of distention and diarrhea, probably due to overgrowth of monilia, an occasional accompaniment of broad-spectrum antibiotic treatment; the side effect responded well to nystatin, an anti-fungal, anti-monilial agent.

Intestinal Absorption of Calcium

It has long been known that vitamin D facilitates intestinal absorption of calcium. Research that should lead to a better understanding of how vitamin D acts and how such deficiency conditions as rickets and osteomalacia are produced was reported in the past year by other Institute-supported investigators. In this study, the grantees showed that administration of vitamin D to rachitic chicks induces formation of a protein in their intestinal mucosa that specifically enhances the intestinal absorption of calcium.

Prior evidence suggested that vitamin D may mediate the intestinal absorption of calcium by stimulating the synthesis or operation of a "carrier substance" (which would combine preferentially with calcium in the intestinal lumen and would carry it across the intestinal mucosal barrier), and that this "carrier" may be a protein. The Institute grantees, in earlier studies, reported that a protein-like factor was involved in calcium uptake. Now the investigators have shown that this factor is indeed a protein, that it forms a soluble complex with calcium, and that there is a close chronologic relationship, after administration of vitamin D_3, between the appearance of the factor and the enhanced absorption of calcium.

Gastrointestinal Hemorrhage

In another area of gastrointestinal research, an Institute-supported investigator has obtained experimental evidence that a blood-borne mechanism, in addition to direct, mucosal irritant factors, may be responsible for aspirin-induced gastric bleeding. There have been numerous observations, clinical and experimental, demonstrating a causal relationship between gastrointestinal bleeding and ingestion of salicylate compounds. Previous research has shown an erosive effect of acetylsalicylic acid on the gastric mucosa and direct evidence of mucosal irritation after aspirin ingestion. This, in turn, has led to doubt regarding the ability of salicylates to cause gastrointestinal hemorrhaging by other than direct mucosal irritation.

In their experiments, the grantees succeeded in inducing bleeding in isolated, denervated stomach pouches (Heidenhain pouches) of dogs after oral administration of salicylates. Similar observations have been made previously by others using innervated Cope pouches, but the observed bleeding was not quantitated, and in such pouches the action of nervous stimuli conveyed via the still intact nerve supply, cannot be ruled out. The grantees found that pouch bleeding did not occur at the initial salicylate dose level, but was significant at a larger dose level. During the third *control* period the mean daily blood loss from gastric pouches was 0.292 cc, compared to a mean of 3.12 cc during the third *treatment* period. Choline salicylate had no significant effect on pouch bleeding. Thus, because bleeding occurred in the denervated, isolated pouches (which were never in direct contact with the drug) as a result of acetylasalicylic acid delivered to the main portion of the stomach, the Institute grantee's findings suggest that a *blood-borne* mechanism, as yet unidentified, may be responsible for gastric bleeding in some cases. Findings such as these prompted the National Institute of Arthritis and Metabolic Diseases to sponsor a conference, last summer, on the possible untoward effects of chronic administration of salicylates.

Morphologic Changes In Human Intestinal Mucosa During X-Ray Therapy Found Transitory

An important forward step affecting X-ray therapy resulted from research supported by this Institute this past year. Studies by NIAMD grantees described morphologic changes which occur in the human intestinal mucosa during abdominal X-ray therapy.

In these morphologic studies of the intestinal tract, the investigators showed that extensive tissue damage of the small intestinal mucosa of man is regularly induced by therapeutic doses of X-rays to various abnormal growths in the abdominal region. The investigators found, however, that this tissue damage not only was associated with surprisingly few symptoms but also was rapidly reversible. Moreover, the damage appeared to be localized to the field of irradiation.

Biopsies obtained from outside the field of irradiation remained normal throughout X-ray therapy, and gastrointestinal symptoms were minimal or absent in all patients. The observed morphological changes also reverted to normal two weeks following cessation of X-ray therapy.

Ulcerogenic Tumors of the Pancreas

In the past year, investigators supported by this Institute also developed a laboratory, bioassay technique that has proved extremely accurate and useful in the diagnosis and surgical management of patients suffering from ulcerogenic tumors of the pancreas. Normally, the hormone gastrin which, once released into the circulation, stimulates gastric secretion of acid and pepsin, is produced in the stomach mucosa. A specific type of tumor of the pancreas is also known to release a gastrin-like substance into the circulation, which is capable of stimulating a constant overproduction of gastric secretions, thus leading to peptic ulcer production.

Utilizing the new technique, the Institute-supported grantees were able to detect an excess of this gastrin-like hormone (which stimulates gastric acid and pepsin secretion and thus induces ulcer formation) in the blood, gastric juice or urine of patients with ulcerogenic tumors of the pancreas. In these studies, the new diagnostic technique has shown a positive result preoperatively in all patients with an ulcerogenic tumor. In addition, the investigators found the technique useful as an aid to the surgeon in determining in advance the most appropriate operative procedure. In each case in which the diagnosis of ulcerogenic tumor was established by utilizing this new laboratory technique, the investigators reported, the diagnosis was also substantiated by biopsy.

Liver Disease

Fatty Livers

Past Institute-supported studies have indicated that excessive alcohol ingestion can lead to development of fatty liver in man *despite* a concurrent adequate dietary intake. The origin of the fat accumulated in the human liver, however, has not yet been reported, whereas in rats, conflicting findings have been published.

In a new study involving five volunteer subjects, Institute-supported investigators now have found that fat which accumulates in the liver under certain conditions differs markedly from that found in body fat depots. Following ethanol (alcohol) ingestion with a fat-containing diet, it was found that the fat which accumulated in the liver was composed largely of fatty acids contained in dietary lipids. When ethanol was ingested with a low-fat diet, the fat in the liver had a large component of endogenously synthesized fatty acids. Thus, the Institute grantees concluded that the fatty acid composition of the alcoholic fatty liver is largely determined by the nature of the diet ingested with the alcohol. These findings are of significance in that they provide an insight into the pathogenesis of the alcoholic fatty liver and indicate that regardless of the lipid content of the diet, alcohol *per se* in even moderate amounts is the prime factor which can lead to the production of a fatty liver.

Acid Mucopolysaccharides in Chronic, Progressive Liver Disease

Although the causes of active progressive chronic liver disease in man are as yet unknown, it has been suggested that a possible mechanism may be related to the marked alterations of hepatic connective tissue ground substance which

have been observed in this type of human liver disorder. Since acid mucopolysaccharides are a past of this substance, an Institute grantee undertook a study of changes of acid mucopolysaccharides in human liver disease.

In this study, the relationship between liver disease and hepatic acid mucopolysaccharides was examined in 666 patients. Histochemically demonstrable acid mucopolysaccharides were detected in increased amounts and at abnormal locations in those types of hepatic injury which were usually, though not invariably, followed or already accompanied by cirrhosis. Those types of hepatic lesions which were not associated with the accumulation of acid mucopolysaccharides were not regularly followed by fibrosis and cirrhosis.

Based on these findings, demonstration of increased amounts of acid mucopolysaccharides in liver biopsies can be of practical diagnostic and prognostic importance for predicting the likelihood of development of liver fibrosis or cirrhosis. Furthermore, demonstration of these acid mucopolysaccharides could serve as one of the objective criteria for determining the effectiveness of any therapy designed to prevent cirrhosis or to suppress fibroblastic activity.

EXCHANGE TRANSFUSION IN SEVERE HEPATITIS

An estimated 1200 patients die each year of acute hepatitis in the United States. The life of one patient apparently dying of acute hepatitis has been saved, however, by Institute-supported scientists in Boston who employed experimentally massive exchange blood transfusions. This procedure, used as a last resort measure on two successive days, resulted in unmistakable clinical improvement within 48 hours, gradual recovery, and discharge from the hospital six weeks later.

It is noteworthy that a group of investigators in South Africa reported almost simultaneously, similar successes with the same procedure in seven of eleven such patients. Although such an extreme measure as exchange transfusion should be reserved for extremely ill hepatitis patients who do not respond to more conservative therapy, the gratifying results obtained by the Boston scientists justify further exploration of this form of therapy.

Outlook

Although this resume of research progress in gastroenterology encompasses but a small portion of the NIAMD-financed research in this extremely broad field, it demonstrates the diversity and productivity of the many investigations conducted and supported by the Institute. These and other research findings are systematically uncovering numerous promising and new scientific leads and approaches in the search for improved methods of treatment and diagnostic techniques for the millions of individuals disabled by and afflicted with gastrointestinal diseases and disorders. Some of the basic mechanisms of these diseases have been clarified; many as yet elude medical research.

The task before medical science in this respect is not easy, however promising the future. Many factors and problems related to gastroenterologic diseases remain to be resolved. There still exists an urgent need for the infusion of additional research workers into the field, a need which the NIAMD will endeavor to fulfill through its continued support of research and research training in centers across the country. A continuing, broad scale and aggressive program of research is essential if we are to build upon our fund of biomedical knowledge which is the primary source for all advances against human disease and if we are to capitalize on it for more effective application to treatment of these diseases of broad popular and economic impact.

Special Report: Diabetes

Final solution to the problem of diabetes will depend upon an understanding of the more fundamental mechanisms at the root of the disorder, and the main thrust of Institute efforts in diabetes is in this direction. During the past year, studies conducted in Bethesda or supported by this Institute and carried out in other biomedical research centers have continued to increase in a very meaningful and useful way the body of knowledge concerning this complicated disease. Institute scientists and grantees have broadened their fundamental studies of the pathology of diabetes, of the action of insulin, and of the many biochemical and physiological changes which occur in body cells and fluids of diabetic patients.

The gains that have been made are especially significant in the light of recent figures released by the National Center for Health Statistics, which forcefully bring to mind the widespread occurrence of diabetes. It is now estimated that there are approximately four million diabetics in the United States. Furthermore, another five million other persons living today in our country are listed as potential diabetics, persons who may develop the disease sometime during their lives. The total number of persons in the world suffering from diabetes is approximately 30 million, while more than a quarter of the earth's population is believed to carry the hereditary gene for this disease.

A complex disorder, for which there is no known cure, diabetes ranks seventh in the list of diseases that cause death. It affects individuals predisposed to the disorder by their hereditary background. As a result of the body's inability to metabolize carbohydrates normally, the diabetic is inefficient in converting carbohydrates into heat and energy required for normal body functions and in storing them in the form of glycogen. The carbohydrates, converted into glucose, accumulate in the blood and spill over into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with derangement in the metabolism of fats and proteins.

In its severe form, diabetes rapidly progresses to a state of grave metabolic derangement, called keto-acidosis, which may result in coma and death unless controlled by insulin administration. In its less severe form, diabetes will result in accelerated degeneration or hardening of the arteries, with 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 those affecting blood vessels, peripheral nerves, and the eyes, tend to develop relentlessly.

Juvenile Diabetes

Diabetes can be divided into two clinical types—juvenile diabetes and maturity-onset diabetes—which have different prognoses, somewhat different treatment, and related, but possibly dissimilar, causative mechanisms. In juvenile diabetes the onset of the disease frequently occurs during childhood or the teens. Although the great majority of such patients can be maintained with regular insulin injections, life expectancy of the juvenile diabetic is considerably shortened.

It has recently been proposed that the inheritance and development of diabetes may be mediated through a structurally abnormal insulin. This concept has gained support during the past year from the work of an Institute-supported investigator at the University of Colorado. He has shown that insulin isolated from the blood of diabetic children is significantly more resistant to destruction by an insulin-specific enzyme than is insulin derived from normal individuals.

This finding suggests that there is a genetically determined difference in natural insulin which in the juvenile diabetic contributes significantly to the underlying biochemical disorders of diabetes. It would appear that resistance of juvenile diabetic insulin to the enzyme is a function of some difference in the insulin molecule itself, perhaps a structural change which affects the active contact site for the enzyme.

Diabetes resembling the human *maturity-onset* type has been described previously in hamsters and dogs, and in recent years, Institute grantees have reported it in a new animal model, heretofore unknown in the United States, the Egyptian sand rat. Institute-supported investigators at the Jackson Laboratory in Bar Harbor, Maine, now have described a metabolic disorder closely resembling human *juvenile* diabetes which has appeared as a new genetic mutation in inbred mice. These diabetic animals exhibited a severe disease syndrome with onset at an early age and a shortened life-span. Because the disease closely resembles juvenile diabetes in man and is readily reproducible, the new strain of mice will provide a much-needed experimental animal model for research on juvenile diabetes.

The Jackson Laboratory scientists already are conducting further studies of the chemistry, endocrinology, pathology, and genetics of the diabetes mutant. Such studies may well provide diabetes investigators with information on many of the unanswered questions about the etiology of diabetes.

Diabetes in the Pima Indians

Institute scientists are continuing their studies of the Pima Indians of Arizona, a population group found recently to have the highest rate of diabetes ever reported in a circumscribed, and otherwise normal population group. Intensive studies are underway to investigate the mode of inheritance of diabetes, the natural history of the disease and its complications, the role of diet and other environmental factors, and the effect of various therapeutic measures.

The investigators' most recent findings indicate that the effects of child bearing do not account for the higher prevalence of diabetes among women. These findings are at variance with previous diabetes clinic studies by other scientists, principally in England, which have supported the hypothesis that pregnancy precipitates diabetes. Contrary to expectations, the prevalence of diabetes, especially in the younger age groups, was found to be somewhat higher in Pima Indian women who have *not* borne children than in those who have borne seven and more. The Institute scientists suggest that in previous studies which linked diabetes to pregnancy there was more likely an indirect association with obesity.

Insulin Action

One of the greatest challenges in diabetes research is the fact that 45 years after the discovery of insulin much disagreement still exists about the mechanism of action of this important hormone. It is known that insulin's single most important action is to facilitate the entry of glucose into the cells of the body. An understanding of the precise mechanism by which insulin accomplishes this task is essential to full solution of the diabetes problem.

It has been postulated that insulin may act primarily by initiating a disturbance at the cell surface which produces widespread structural changes. Such changes, it is theorized, would lead not only to increased penetration of glucose and other substances into the cell interior, but might also explain several other known effects of insulin. This hypothesis has been strengthened by recent studies by grantee-scientists at Mount Sinai Medical and Graduate Schools, New York, and at Johns Hopkins University, Baltimore. The New York investigators have shown that radioactively labelled insulin binds largely to the boundary membrane of the muscle cell. They have suggested that this action of insulin may facilitate the entry of glucose, electrolytes, water, and amino acids into the cell via a hormone-sensitive, possibly contractile, system which might also account for the known stimulating effects of insulin on protein synthesis. The Baltimore scientists have added support to this proposal by showing that insulin has an *immediate* effect on potassium and sodium movement in and out of rat muscle tissue. This finding implies that insulin acts on the outer boundary of muscle cells and is in line with the proposal that it acts primarily on the cell membrane.

Prediabetes

It has been generally accepted that abnormal carbohydrate metabolism, as evidenced by elevated blood sugar levels and abnormal glucose tolerance tests, is the initial sign of clinical diabetes, and that small blood vessel disease develops as the disease progresses. Grantee-scientists at the University of Texas Southwestern Medical School in Dallas, however, have unearthed evidence to suggest that the reverse might be true; specifically, diabetes may be primarily a disease of the vascular system and not simply a disorder of carbohydrate metabolism.

These investigators have found that significant small blood vessel disease in muscles expressed in the form of marked thickening of the basement membrane of capillaries, which is characteristic of overt diabetes, appears in at least 50 percent of genetically prediabetic subjects prior to the onset of carbohydrate abnormalities and in practically all diabetic patients thereafter. Prediabetic subjects, persons genetically destined to develop diabetes sometime during their lives, were defined in this study as those having two diabetic parents, normal fasting blood sugar levels, and normal glucose tolerance tests.

These findings suggest that small blood vessel basement membrane thickening may represent the primary lesion of diabetes, followed only secondarily by carbohydrate derangements. The significance of this observation is that diabetes investigators are now afforded a new angle of attack, a direction for research efforts which may be much more fruitful in determining the fundamental cause of diabetes than previous studies directed mainly toward the abnormality in carbohydrate metabolism.

Complications of Diabetes

Although the "control" or management of the clinical symptoms of diabetes has improved dramatically during recent years, complications such as heart disease, failing eyesight, hardening of the arteries, impaired kidney function, diabetic retinopathy and diabetic neuropathy continue to plague the older diabetic who has had the disease for many years. While concentrating primarily on the cause and prevention of the basic disease, researchers today are also vitally interested in these complications in the older diabetic, inasmuch as his life expectancy and function depend on them to a large extent.

Diabetic neuropathy, a condition characterized by lesion in the peripheral nervous system, is reported to occur in four per cent of diabetic patients, but undoubtedly occurs in a less severe form much more frequently. The exact cause for such lesions has not been established. An Institute-supported investigator at Massachusetts General Hospital in Boston has now obtained evidence to suggest that a little-known chemical pathway involved in sugar metabolism (the conversion of glucose to fructose via sorbitol) may be overactive in the sciatic nerve and spinal cord of rats with experimentally-induced diabetes. The existence of such a hyperactive abnormal biochemical mechanism in these tissues in diabetes, coupled with the marked local accumulation of its products, may have major implications for the development of diabetic neuropathy. It is known that in animals with galactosemia, another disorder of carbohydrate metabolism, such as an aberration of biochemical pathways is involved in the development of cataracts. The present fiindings suggest that a similar mechanism may be operative in diabetic neuropathy.

Maturity-Onset Diabetes

A number of factors have been identified as predisposing an individual to diabetes. It is well established that those persons most likely to develop the disease are overweight, over the age of 40 years, relatives of diabetics, or mothers of large babies. During the past year Institute grantee-scientists suggested that idiopathic edema may also be a predisposing factor for diabetes.

Idiopathic edema is a term used to describe localized or generalized swelling, asociated with accumulation of fluid in certain body tissues, the cause of which is unknown. The disorder most often affects women nearing the menapause who are overweight and emotionally tense and unstable. Studies of such patients now have suggested that idiopathic edema may be an early sign of diabetes. Scientists at the University of Vermont have found that these patients show both an abnormality of the small blood vessels and impaired carbohydrate tolerance, conditions which are known to precede the onset of clinically apparent diabetes. Their findings suggest that idiopathic edema may be an early sign of latent or mild asymptomatic diabetes. The investigators recommend that carbohydrate tolerance should be evaluated in idiopathic edema patients periodically, and treatment appropriate to the severity of any diabetic abnormality which may be found should be initiated.

Significance of Large Babies

Other investigators at Boston City Hospital have questioned the concept that women who give birth to large babies (more than nine pounds) are likely candidates for diabetes. In a study of 5,534 pregnant women who were followed to term, elevated blood sugar levels were seen only in *overweight* women who gave birth to large babies. Overweight women with infants of average birth weight, as well as normal weight women with large babies had no such blood sugar elevation. This finding implies that it might be possible to make a more accurate clinical distinction than is now made between potential mothers who are most likely to develop diabetes and those who are not likely to develop the disease.

Autoimmune Diabetes

Grantee-scientists at the University of California, San Francisco, have obtained evidence to suggest that autoimmunity, the development and persistence of antibodies capable of action against one's own tissues, may play a role in

diabetes. They have reported that an autoimmune diabetes closely resembling the early juvenile type can be induced in rabbits by immunizing them with bovine insulin.

The investigators had shown earlier that rabbits immunized with bovine insulin developed antibodies directed against their *own* endogenous insulin. It was observed subsequently that several of these animals not only produced such antibodies, but also, as a result of the autoimmune phenomenon, became acutely diabetic. This observation raises the possibility that autoimmunity may not only be a contributing factor to the diabetic state in insulin-treated human subjects, but may also be an important underlying cause of the disease. At the present time, however, evidence that autoimmunity may play a role in the causation of diabetes is equivocal, and further studies will be necessary to determine its role, if any.

Outlook

The story of diabetes, and its control, is one of the more heartening in the annals of medicine. Thanks to the fruits of past research, most diabetic patients today can enjoy a normal home and family life and can work with only minor complications. Continuing advances depend upon investigations of the natural history of the disease and of its complications in diabetic populations, of genetic factors in various diabetic animals, and of insulin action. It is in these areas that research has made greatest progress in recent years. New research areas of particular interest and importance are determination of the basis for development of the ocular, neurologic and vascular complications of diabetes and investigation of the diagnostic significance of capillary membrane thickening for detection and possible preventive therapeutic management of individuals destined to develop diabetes in future years. Progress in these two areas will contribute with particular effectiveness toward ideal control of this complex metabolic disorder of genetic origin.

Special Report: Arthritis and Rheumatism

Today, one out of every 15 persons in the civilian noninstitutional population of the United States suffers from some form of arthritis. This represents a total of 13 million Americans, most of whom are older people, women, persons in low income groups, and residents of rural farm areas. Every year, an estimated 12 million days of work are missed because of arthritis, costing the economy about $220,000,000. An additional $300,000,000 in salaries is lost by arthritics who are unable to work at all because of the disease.

As many as 30,000 persons with arthritis apply each year for disability benefits under the Social Security Administration's Old-Age, Survivors and Disability Insurance. During the latest calendar year for which figures are available, payments under this program to persons whose primary cause of disability was arthritis totaled $85,000,000. An additional $47,000,000 is paid to arthritics annually by the Welfare Administration's Aid to the Permanently and Totally Disabled.

Adding to this the cost of hospitalization, physicians' visits, drugs, physical therapy, nursing home care, and other items such as Federal and State income tax losses, authorities now estimated a total price tag of two billion dollars per year. The suffering in terms of human misery and economic privation is impossible, of course, to assess.

Through its intramural and extramural programs, the National Institute of Arthritis and Metabolic Diseases (NIAMD) stands in the forefront of the research battle against arthritis. This report summarizes the results of another year of research efforts on the problem of eradicating the suffering and loss of productivity caused by arthritis. Research has continued on the ever challenging question of what causes these diseases, as well as into improved methods of treating them and preventing disability.

Rheumatoid Arthritis

Of all the major forms of arthritis, rheumatoid arthritis is the most crippling and the most puzzling in terms of etiology. In their search for a causative agent, investigators are encouraged, however, by recent evidence suggesting that mycoplasma, a type of microorganism, somewhere between bacteria and viruses in size and other properties, may be involved, directly or indirectly, in the etiology of this disease. The increasing interest of investigators in mycoplasma and the

rapid development of research findings made it essential that a group of knowledgeable investigators be brought together not only to exchange information but to examine critically the evidence supporting a relationship of this organism to rheumatoid arthritis, and to stimulate further research.

The Institute, therefore, joined forces last February with the Division of Research Grants, NIH, to co-sponsor a working conference in Chicago on "The Relationship of Mycoplasma to Rheumatoid Arthritis and Related Diseases." About 35 authorities in the field met to discuss the mycoplasma, diseases in animals and man known to be associated with them, the evidence for associating them with human arthritis, and possible ways in which the organisms and their host might interact to produce the disease. Among the resulting proposals were that standard reference sera (immune blood fractions capable of reacting with mycoplasma) be made available in research banks for the use of investigators, and that medical and veterinary resources for the study of mycoplasma be brought together, where possible. Scientists at the meeting concluded that although the evidence linking mycoplasma infection to rheumatoid arthritis is fragmentary, it is sufficient, nevertheless, to encourage further research.

Another group of microorganisms, the Bedsonia, have commanded a considerable amount of research attention this past year. A team of investigators at the University of California produced arthritis in monkeys by injecting them with Bedsonia organisms isolated from human patients with Reiter's syndrome, a disease related to rheumatoid arthritis. They were then able to recover Bedsonia from all the infected joints and from various internal organs of the experimental monkeys.

The Bedsonia viruses have been reported to cause polyarthritis in lambs. This fact plus the knowledge that they cause human trachoma, inclusion conjunctivitis, and lymphogranuloma venereum led the investigators to suspect that they might contribute to the development of Reiter's syndrome, a triad of urethritis, arthritis, and conjunctivitis. If furher sudies confirm initial findings, this work may eventually have important bearing on a whole series of disorders that have arthritic manifestations, including rheumatoid arthritis.

A DISTINCTIVE RHEUMATOID ARTHRITIS CELL

A study conducted by NIAMD and National Center Cancer Institute investigators has provided new information about certain cells which at times pose a problem in the differential diagnosis of rheumatoid arthritis. The investigators have described a distinctive multinucleated synovial giant cell in rheumatoid arthritis. The cells were present in the knee joint synovia of 9 out of 19 patients with active disease and positive serologic tests for rheumatoid arthritis. None were found in 9 seronegative rheumatoid arthritis patients or in a series of control cases. The giant cells were also observed in joints other than the knee. They can usually be readily distinguished from multinucleated plasma cells, foreign body giant cells, and Touton cells that also occur with some frequency in rheumatoid arthritis.

TWIN STUDIES OF RHEUMATOID ARTHRITIS

Two factors that have long been thought to be associated in some way with the onset of rheumatoid arthritis are heredity and emotional stress. Institute supported investigators at the University of Rochester have now obtained evidence from a study of the disease in twins that pschologic stress may play a greater role in determining onset of the disease than heredity.

The investigators studied eight sets of female identical twins, in which only one twin in each set was affected with rheumatoid arthritis. It was found that all the affected twins had undergone a series of life events that were demanding and restricting, during which time they developed their first symptoms. The unaffected twin, in every case, had no comparable experience. These findings are consistent with the conclusions of a very extensive epidemiologic study by Institute investigators during 1963–65 that inheritance does not play an active role in the pathogenesis of rheumatoid arthritis.

AUTOIMMUNITY

One of the principal theories on the pathogenesis of rheumatoid arthritis is the concept of autoimmunity. This theory holds that the body, for some unknown reason, produces abnormal antibodies that are directed against its own tissues rather than against foreign material. Part of the evidence supporting this con-

cept is the elevated gamma globulin (antibody) content of the blood in rheumatoid arthritis patients and the antibody-like nature of the characteristic rheumatoid factor—complex, specific proteins found in the serum of patients with rheumatoid arthritis.

A potent argument in the past against the antigen-antibody pathogenesis of rheumatoid arthritis, however, has been the frequent occurrence of arthritis in patients with a disease called agammaglobulinemia, which is associated with a deficiency of antibodies. Rheumatoid factor cannot be found in the blood of these patients, and immune gamma globulins can be found only in small amounts. Institute grantees at the University of Pennsylvania have now refuted this argument by showing that in agammaglobulinemia, immunoglobulins which are not detectable in the blood may be found in the joint. Their study indicated that in this disease immunoglobulins are apparently produced in demonstrable quantity in the synovial membrane, just as in typical rheumatoid arthritis. This demonstration of an immunoglobulin reaction in agammaglobulinemic arthritis gives further support to the concept of autoimmunity in rheumatoid arthritis.

Institute-supported investigators at the University of Texas have reported a study which offers hope for an effective form of therapy in rheumatoid arthritis and in other diseases caused by immune mechanisms. Adjuvant arthritis (an experimentally induced form of arthritis exhibiting a true, but transitory, immunological reaction and polyarthritis symptoms) was induced in 30 rats by injecting them with Freund's adjuvant. Ten of the rats were treated with rabbit anti-lymphocyte serum, which successfully suppressed the usual arthritic reaction; only one developed a moderate arthritis. In contrast, 20 control rats all developed marked polyarthritis. This important research lead is being followed up with additional studies to determine its possible applicability to treatment of human arthritis.

Further information related to the immunity aspects of rheumatoid arthritis was obtained in a fundamental research study completed by grantee investigators at the University of Pennsylvania. Their study of albumin distribution in selected rheumatoid arthritis patients has indicated that the low serum levels of albumin frequently encountered in these patients are associated with an increased fractional turnover rate of albumin, indicating increased albumin destruction rather than diminished synthesis. This finding is noteworthy in view of the knowledge that corticosteroid drugs, often a necessary form of therapy in rheumatoid arthritis, can further deplete reduced body pools of albumin, and thus may be deleterious to a patient who is already chronically ill.

A study conducted this past year at the New York Downstate Medical Center also concerned the relationship of certain drugs to serum albumin. A grantee investigator there studied a total of 180 commonly used drugs with respect to their interaction with serum albumin. He found that 13 of the drugs, including aspirin and other non-steroid anti-inflammatory compounds, interacted with serum albumin in a unique way. They had the ability to alter the tertiary structure of serum albumin molecules. Since all but one of the thirteen drugs exhibiting this unusual effect are known to be anti-inflammatory, this finding may lead to a valuable means of screening compounds for anti-inflammatory activity.

Another grant-supported study at Duke University has helped explain the anti-inflammatory and fever-reducing effects of aspirin (acetylsalicylic acid), used much more extensively than corticosteroid drugs in rheumatoid arthritis and other arthritic disorders. This finding concerns lysosomes, which are subcellular packets of enzymes found in large numbers in synovial lining cells of rheumatoid joints. It was reported last year that a different group of Institute-supported scientists had shown that a disruption of these lysosomes induces in rabbits an arthritic lesion similar to rheumatoid arthritis in man. Aspirin has now been found to stabilize lysosomes, suggesting that the drug's beneficial effects may be brought about through a lysosomal mechanism.

Aspirin was also the subject of a conference sponsored by the Institute at the New York Medical College last June. This working conference on the "Effects of Chronic Salicylate Administration" brought together approximately 40 medical experts from the United States, England, and Canada to scrutinize the effects of repeated aspirin administration in man and animals and to determine in what specific areas more information is needed. The conferees explored the metabolism, pharmacology, and toxicology of salicylates; their pathologic effects in animals; and the possible relationship of these effects to long-term salicylate administration in patients with rheumatic diseases.

Osteoarthritis

During the past year several significant findings have been reported by Institute-supported scientists regarding osteoarthritis, a common disorder of unknown etiology associated with degenerative changes which alter the mechanical structure of the joints. Investigators at the Medical College of Georgia reported that *Rumalon*, a cartilage-bone marrow extract, is of clinical value in the treatment of osteoarthritis. The cartilage of patients with this disorder is thought to be deficient in chondroitin sulfate, a component of the ground substance of tissues. Thus, a drug capable of stimulating the synthesis of chondroitin sulfate in the affected tissues theoretically would be considered helpful in counteracting the pathologic changes in osteoarthritis. The scientists reported that *Rumalon* stimulates the uptake of radioactive sulphur in human osteoarthritic cartilage, indicating increased synthesis of chondroitin sulfate. This study warrants further investigation of the basic mechanism of action of this extract, as well as continued clinical trials of its effectiveness.

In another approach to this disease, nine German Shepherd dogs with osteoarthritis of the hip were studied in the Orthopedic Research Laboratories of the University of Pittsburgh. The grantee investigators obtained and studied slices of cartilage from the weight bearing and non-weight bearing areas of the arthritic femoral heads and from the distal femoral joints of these dogs. Their observations, along with other experimental evidence, suggest that the cartilage cells (chondrocytes) in the weight bearing area of osteoarthritic hips are synthesizing protein and RNA at a decreased rate in comparison with normal hips. This finding may provide a clue towards our eventual understanding of the fundamental disease process in osteoarthritis.

Fundamental Research on Joints

It has been suggested that contractions of the skeletal muscles may play a role in the development of joints during the embryonic stage. Previous investigations of this theory failed to preserve the exact embryonic environment, however, and the resulting joint deformities could not be attributed solely to the absence of movement. A study carried out by an Institute investigator in Bethesda, in collaboration with a grantee of the National Institute of Child Health and Human Development at Tufts-New England Medical Center, has now shown that joints do not develop normally in chick embryos paralyzed by three different techniques (two different neuromuscular blocking agents and surgical removal of the spinal cord). In striking contrast to the normal joint cavities in control specimens, the paralyzed joint cavities failed to develop and became filled with fibrous tissue which eventually bound the joint elements together. In addition, joint surfaces were flattened and distorted. That these abnormalities were due to paralysis *per se* (absence of fetal muscular contractions) was evidenced by the fact that the three treatments produced effective paralysis by different mechanisms, as well as producing identical joint abnormalities. Thus, the possibility of a common, direct toxic action on the joints was excluded. Results of the study clearly indicate that embryonic movement plays an important role in the formation of joints.

Some biochemical and biophysical aspects of joint stiffness were clarified in another study by a grantee investigator at the University of North Carolina School of Medicine. It is generally known that even temporary immobilization of normally movable joints can result in a permanent loss of motion. It is also appreciated that immobilization of joints surrounded by edematous soft tissue often produces joint stiffness more quickly and severely than immobilization of nonedematous extremities. The actual mechanism, however, by which range of motion is lost and the exact changes in joint structures which are responsible for decreased mobility are unknown. In this study, the investigator found gross, microscopic, and biochemical evidence that new collagen synthesis is the fundamental process in the pathogenesis of joint stiffness. He found that flexion contractures of canine and rat knee joints produced by experimental fixation in the flexed position are the result of important changes in collagenous tissue on the flexor side of the joints. The study also showed that surgical removal of newly synthesized collagen from strategic areas around stiff human interphalangeal joints produces immediate relief of flexion contractures. Long-term results, however, of surgical removal of excess collagen from stiff joints have not been satisfactory, it was concluded, because of *subsequent* collagen synthesis during the healing process.

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Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a grave, generalized disease which is manifested by structural and functional changes in the skin, joints, and internal organs. Young women are most frequently affected, and the disease is found most often in the 20–40 year age group. For many years, research on this insidious inflammatory connective tissue disorder was hindered by lack of an experimental animal model. Then in 1961 a strain of highly inbred New Zealand mice was discovered which developed a disease resembling human SLE without evidence of any concurrent infection or dietary deficiency. Further studies of these animals by grantee investigators at the University of Southern California have now provided additional clinical and pathological data which emphasize the close similarity between this model and the human illness.

Findings in the mice included typical LE cells (giant cells considered pathognomonic or characteristic for lupus erythematosus), antinuclear antibodies, hemolytic anemia, proteinuria, and nephrosis with kidney failure—all of which are associated with the human disease. The incidence and severity of the lesions were much more prevalent in female than in male mice, a finding which is also consistent with human SLE. Further investigation of this heretofore unavailable animal disease model should provide clues to its cause and development, should lead to controlled studies of various methods of treatment, and may provide keys to a better understanding of the human disorder.

Although the cause of systemic lupus erythematosus is not known, evidence points to an abnormal antibody reaction. Circulating antibodies that are capable of harming the body's own tissues have been found in SLE patients. It has also been suggested that these antibodies may combine with the products of tissue breakdown to form immune complexes potentially harmful to organs such as the kidneys. Institute-supported investigators at Washington University in St. Louis have now found further evidence to support this theory. Their immunofluorescent studies have detected extensive deposits of bound gamma globulin in the skin lesions of SLE patients. It is suggested that such lesions may be one source of antigens, in the form of tissue components, which are released into the circulation during tissue damage. These antigens then combine with circulating antibodies to form immune complexes capable of damaging a variety of organs in the patient.

Scleroderma

Scleroderma is a serious, systemic disease characterized by fibrous thickening of the skin and by scattered hardening of internal organs. Its etiology remains unknown, and there is no satisfactory form of treatment. Evidence has been obtained in an Institute-supported study at the University of Texas, however, that an underlying blood-vascular mechanism may play an important role in the development of this disease. The investigators studied biopsies of muscle from 8 patients with scleroderma who had no evidence of muscle involvement. A capillary abnormality, lamination of the basement membrane, was found in all the specimens obtained. Sixty-five per cent of all capillaries were involved in these patients, the overall frequency or number of blood vessels per volume of tissue was decreased, and the average diameter of blood vessels was slightly increased. It was concluded that a distinctive morphologic change occurs in a high proportion of the capillaries of the skeletal muscle of patients with scleroderma, a new finding that may be significant in the pathogenesis of this disease.

Gout

One important cause of acute, extremely painful, and sometimes chronic destructive arthritis is gout, an inherited metabolic disorder associated with an increased amount of uric acid (hyperuricemia) in the blood and tissues of those afflicted. In this disorder, uric acid crystals are deposited in and around the joints, resulting in inflammation, severe pain, and eventual destruction of normal joint structure. In especially severe cases, permanent crippling or severe kidney damage, or both, may result.

An Institute-supported study by investigators at the University of California Medical Center has shown that a high percentage of patients with gout also have calcification of cartilage, especially in their knees. A study of 58 patients led the investigators to postulate that the calcification is a secondary manifestation of gout, caused by the deposit of sodium urate crystals around the joints. Calcification of cartilage occurs with a number of conditions related to hyper-

calcemia (abnormally high calcium concentration in the blood), including vitamin D intoxication and hyperparathyroidism. It can also occur after trauma, infection, or degenerative changes, as well as in gout, ochranosis (another metabolic disease), and in pseudogout.

At the present time, gout can be the best controlled of all the arthritic diseases. Treatment aims at controlling excess uric acid accumulation in the body, and preventing or relieving the recurrent painful attacks. Potent drugs developed during the past decade (uricosuric drugs) are used to rid the body of its excess uric acid via the urine, thus preventing a build-up of harmful crystal deposits. These drugs, notably probenecid and sulfinpyrazone, are the mainstay of long-term maintenance treatment in gout. Present research emphasis is on development of methods of early diagnosis and further improvement in management so that deformity and such complications as described above can be prevented.

Outlook

This brief review of some recent research accomplishments in the field of arthritis and rheumatism is obviously not all-inclusive. It is indicative, however, of the increasing velocity of medical science's attack on this debilitating group of diseases, and of the significant stimulus provided by the National Institute of Arthritis and Metabolic Diseases. The past year has yielded a number of exciting findings that offer hope to millions of sufferers, that greater understanding of these conditions will bring with it improved methods of treatment and long-term care.

Special Report: Chronic Kidney Disease

Introduction

Recently, the National Institutes of Health, along with its long and active interest in the development of knowledge concerning kidney disease, has mounted a dynamic program of research on kidney transplantation and kidney substitutes such as the artificial kidney and peritoneal dialysis.

Three of the National Institutes of Health, the National Institute of Arthritis and Metabolic Diseases (NIAMD), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Heart Institute (NHI) have categorical and basic research interests in the several aspects of kidney research. For example, studies relating to immunology and the infectious origin of kidney disease fall within the research purview of the NIAID, metabolic and urological, within the concern of NIAMD, while hypertensive problems are the research responsibility of the NHI. This report presents some of the problems and recent research progress in kidney disease.

The Kidney

The importance of the kidneys can be judged in part by the fact that they receive about one-quarter to one-fifth of the blood volume pumped by the heart. By selective excretion of certain substances and reabsorption of others, the kidneys play an extremely important role in regulating the composition of blood and other body fluids. They continually process blood to eliminate detrimental waste products of metabolism. The kidneys help to regulate the chemical environment of the body cells by regulating the concentration and composition of salts and the amount of water in the blood and tissues. The kidneys also produce substances which are important in regulating blood pressure and in stimulating the bone marrow to produce blood cells.

Causes of Kidney Disease

Latest available figures from the Public Health Service's National Center for Health Statistics indicate that 24,697 Americans died of kidney disease in 1964. These figures do not include deaths attributed to conditions such as hypertension or stroke which may be secondary to an underlying kidney ailment. Experts who comprise the Scientific Advisory Board of the National Kidney Foundation estimate that the actual number of deaths in which kidney disease is the primary cause approaches 100,000 each year.

The term kidney disease encompasses a number of conditions of varying causation which attack the kidneys. Among the leading causes of kidney diseases are:

1. *Hypersensitivity diseases* in which kidney tissue is destroyed by an immune reaction initiated by any of a number of causes, including streptococcal infection.
2. *Infections* in which kidney tissue is attacked and destroyed by microorganisms.
3. *Circulatory diseases* in which the kidney is affected as a result of disease of the blood vessels or the blood itself.
4. *Metabolic diseases* in which the kidney is secondarily affected, such as in diabetes or gout.
5. *Developmental disorders* in which the kidneys fail to develop or develop in abnormal fashion.
6. *Obstructive conditions* in which urine flow is blocked with resultant pressure damage to the kidney and repeated infections.

One characteristic common to most of these diseases is their tendency to eventual progression to a common end-stage—the clinical syndrome of uremia. Uremia is the collection of signs and symptoms resulting from the loss of the kidney's normal functions of removing wastes from the body and of regulating the internal chemistry of the body.

Patients with uremia may be divided into two groups, those with acute kidney failure, and those with chronic renal insufficiency. In acute kidney failure, the kidneys are damaged by an acute insult and the symptoms of uremia progress rapidly. The damage may be reversible, however, and after a short period the kidneys may heal and regain normal function. On the other hand, chronic kidney insufficiency is brought on by gradually progressive destruction of the kidneys from which they do not usually recover. In these cases the kidneys never regain the ability to reverse the trend toward ultimate, fatal uremia.

TREATMENT OF KIDNEY FAILURE

It follows that the natural course of these two types of kidney failure dictates the goals of therapy. In acute, potentially reversible kidney failure, the primary objective is to sustain normal life processes in the patient for the relatively short period of time during which his kidneys cannot function. Eventually recovery may be complete, in which case no further treatment is needed, or the disease may progress and become chronic. In cases of chronic kidney insufficiency, the problem is much more difficult, and some measures of continuing therapy are necessary.

The two substitutes for kidney function which have come into use are peritoneal dialysis and the artificial kidney (hemodialysis). Both methods employ the same basic principle of dialysis: dissolved substances found in high concentration in the fluid on one side of a semi-permeable membrane will tend to pass through this membrane into the fluid on the other side where these substances are absent or found in lower concentration.

Kidney transplantation is a technique whereby a functioning kidney from a donor is transplanted into a patient who has lost his kidney function. Although this procedure is at present still in its experimental stage, it shows considerable promise. With continued research, it is hoped that kidney transplantation, supplemented by efficient methods of hemodialysis until the patient is ready for an operation or until a suitable kidney is available for transplantation, will make fatal chronic uremia a menace of the past.

TRANSPLANATION IMMUNOLOGY: EARLY PROGRESS IN BREACHING MAJOR BARRIERS

The living body's implacable determination to destroy any intruder—a life-saving graft as well as a life-threatening microbe—remains the principal major barrier to successful kidney and other organ transplantation.

The surgical techniques for transplanting kidneys have in large part been developed and are constantly being refined. Today, most kidney transplant operations are surgical successes, technically. The immune response of the body, however, if not suppressed, usually destroys the transplanted tissue within a short time.

When a kidney is transplanted between identical twins, no immune response occurs because the donor's and the recipient's tissue cells, having a common genetic origin, are chemically identical. Kidney transplants between identical twins have, therefore, been generally successful.

The body ordinarily defends itself against a graft, as against any foreign substance, by making counterattacking substances (antibodies), and by mobilizing specialized, defensive processes. This immune response is triggered by antigens in the graft tissue. In a series of complex events the unwelcome graft is attacked and ultimately destroyed.

Progress has been made over the years in the science of transplantation immunology. The discovery in 1901 of the AB blood groups made possible the matching of erythrocytes, or red blood cells, so that today typing and effective pairing of donors and recipients make blood transfusion a successful medical tool.

The problems involved in tissue transplantation are considerably more complex. Considerable achievements have, however, been made. A number of transplantation, or histocompatibility, antigens has been identified. They are found in both body tissues and leucocytes (white blood cells). Some tests have been devised to compare the reaction between the leucocytes of prospective donors and recipients and thereby measure the degree of compatibility between their tissues. Early transplant operations using these leucocyte-matching tests have had a success rate in unrelated donors and recipients approaching the rapidly improving success rate in related persons who, because they are likely to share a number of antigens, are more likely to have a higher degree of compatability. Investigators believe that leucocyte typing may ultimately become the standard means of proper selection of organ donors.

The defensive immune response of the body can be counteracted and the eventual destruction of the transplated kidney delayed or possibly prevented through use of certain so-called immunosuppressive drugs. Whole body x-ray irradiation also can reduce the formation of antibodies. These aids to transplantation prolong the functional life of the transplant, but at the same time may weaken the host's resistance to infection.

In short, progress has been made in the experimental science of tissue transplantation immunology. But much remains to be learned before the replacement of failing kidneys and other organs with new ones can become a reality.

TISSUE TYPING

The National Institutes of Health began to expand its program in tissue transplantation immunology in 1964, when Congress authorized a broad program of research in the field. Grant-supported research projects, intramural studies, and organized developmental work in medical centers and industry have been stepped up in succeeding years. The efforts of many laboratories have been focused on hurdling the remaining barriers through both basic research in immunology and kidney diseases, and through development of a badly needed universal tissue-typing system.

The urgent need, and the short-term goal, of this program is the identification of all the tissue transplantation antigens and their classification according to relative strength. Experimental work has shown that there are apparently only 6 to 10 major transplantation antigens rather than the 15 to 30 which had been predicted on the basis of animal studies. This finding is encouraging, but investigations are being accelerated (1) to make certain that the new number represents all the significant antigens, (2) to isolate those that are the strongest, and (3) to improve the techniques for antigen-antibody detection.

A major requirement of the typing program is specific, high quality antisera (blood serum containing antibodies) for comparing typing results and serologic techniques. The contract supported program of NIAID had produced by the end of 1966 more than 36 liters of antileucocyte antiserum for issuance to tissue-typing laboratories all over the world. Through two contractors (one in Europe, the other in the United States) that are acting as serum banks, the sera are being distributed for further characterization studies, for attempts to fix the total number of leucocyte antigens, for evaluation typing of transplant patients and prospective donors, and for attempts to isolate and purify histo-compatibility leucocyte antigens obtained from tissue culture and other sources.

There has been encouraging evidence that the leucocyte-matching tests apparently do identify the key transplantation antigens. With these typing tests it has been possible to select from a random population unrelated donors whose kidneys provided as good a survival rate and function as kidneys from donors related to the recipients. Further refinement of techniques, however, must occur before the present laboratory procedures can be applied to the selection of patients and donors in kidney transplantation centers throughout the country.

Research on the transplantation antigen-like activity of bacterial fractions gives hope that eventually antigens can be produced from bacteria or cell cultures and substituted—in both typing and matching—for living leucocyte cells, which are difficult to store. They may some day also prove useful in stimulating tolerance to foreign grafts.

ADJUNCTS TO TISSUE TYPING

Because transplants, except between identical twins, are frequently ultimately rejected by the body, the critical problem still is to find methods to reduce—and some day to eliminate—the immune response to grafts. Lasting success depends on matching the recipient's and donor's cells as closely as possible, and then overcoming any remaining minor incompatibility by inducing immunological tolerance in the recipient's body.

Certain immunosuppressive drugs for use in the prevention or control of the rejection phenomenon are being studied. Studies are being conducted to find more effective and less toxic drugs to control the immune response.

Two groups of investigators have produced specific immunologic tolerance to grafts in mice and in dogs by administration of antilymphocyte serum before the transplant operation. This procedure resulted in striking prolongation of the graft and apparently induced tolerance also to second grafts. Another group found that antiserum to thymus prolonged skin graft survival in rats twice as long as antiserum to lymphocytes.

In addition to antilymphocyte serum, total and sub-total body irradiation, cytotoxic drugs, and surgical alterations of the lymphatic system have been used in attempts to reduce or eliminate the lymphocyte population and thus increase tolerance to homografts. These methods, however, also cause undesirable general effects, such as depression of bone marrow and red blood cell formation.

Now selective destruction of *lymphocytes* and a consequent tripling of kidney homograft survival-time in dogs has been achieved by grant-supported scientists. According to this method, radioactive pellets of yttrium are sealed in a Silastic tube and the tube is suspended within the aorta by a single Dacron suture. The yttrium isotope was chosen because of its short half-life and because the beta rays it emits are mainly confined to the immediate area of the implant. Thus, the bloodstream serves to shield the adjacent aortic wall at the same time it is bringing the extremely radio-sensitive lymphocytes within range of the capsule.

Functional survival of the kidney homograft was more than tripled in 10 radiation-implant dogs over that of eight untreated control animals. No permanent survivals were obtained with the short-term radiation employed, but further studies are under way to evaluate longer periods of radiation, and various combinations of radiation and immunosuppressive drugs.

SUPPORTIVE BASIC RESEARCH

Paralleling the efforts to develop reagents, tests, and techniques for applying the knowledge already gained are research projects aimed at understanding the basic immunologic processes of the human body. Intramural projects in Bethesda on immunology focus on such areas as hypersensitivity, mechanisms of the immune response, immunochemistry of serum antibodies and antisera, and induction of delayed hypersensitivity. Many of these studies are closely related to the problems of transplantation.

PROTECTION OF TRANSPLANT

This past year, a grant-supported scientist markedly reduced early failure of kidney homografts by a program of "renal-protective" management. By hydrating living, consanguinous donors immediately before operation, the grantee has been able to reduce significantly early functional failures of kidneys transplanted from the donors. This program of "renal-protective" management was employed to offset kidney damage that begins with anesthesia and is worsened during subsequent surgical manipulation of the organ.

In his study, 10 patients (Group A) received kidneys from donors who were given routine preoperative treatment, while 21 patients (Group B) received kidneys from donors who were given "renal-protective" management: induction of diuresis (increased urine excretion) before anesthesia, strict maintenance of blood pressure during surgery by continuous fluid replacement, and maintenance of diuresis by intermittent injections of the drug mannitol.

There was evidence, too, that "renal-protective" management, coupled with immunosuppressive *pre*treatment of recipients with corticosteroid drugs and azathioprine, enhances survival of grafted kidneys beyond the first two months: overall mortality two to 24 months postoperatively was 60 per cent in Group A patients and 19 per cent in Group B patients.

Recent data from the Human Kidney Transplant Registry clearly show that most graft failures occur within 60 days after transplantation. The present results suggest that such failures may stem from occult renal damage initiated within the donor during nephrectomy, and that such damage may be largely prevented by prehydration and mannitol-induced diuresis in the donor.

Clinical experiences with 100 consecutive non-twin kidney *homotransplants* performed during the four year period from 1962–1966 were recently presented by a group of grantees to the Third International Congress of Nephrology meeting.

The long-term follow-up data obtained from this large number of patients permitted some interesting comparisons between transplants from related living donors (RLD) and those from cadaver donors. These comparisons, based on duration of excellent kidney function rather than patient survival-time, revealed plateaus in kidney function at 12 months for cadaver kidneys, and 18 months for those from related living donors. This function was maintained for 30 months in 41 per cent of the cadaver kidneys, and for 36 months and over in 58 per cent of the RLD kidneys.

The study also catalogues some signs and events occurring within weeks of transplantation that, in many cases, enable one to predict the long-term fate of the transplant, whether cadaver or RLD in origin. For example, if the transplant undergoes a rejection crisis within the first week, or if rejection crises occurring during the first four months are severe enough to require the use of an artificial kidney, the odds that the transplant will continue to function beyond one year are practically nil. If no rejection crises occur during the first four months, prospects are excellent for continued good function for a period of several years—up to three and one-half years in this study. Predictions between these two extremes can be based on whether or not rejection crises, however severe, can be brought under control within 30 days.

FUTURE PROGRAM DIRECTION

Organ transplantation is still an experimental science, despite the limited success with kidney grafts. And there are many unanswered questions, such as: What mechanism is involved in the survival of a transplant? Why do failures occur? How do antibodies destroy an organ?

Multidisciplinary studies of the immunologic and therapeutic means available for achieving permanently successful grafts must continue to be pressed. Medical science must continue to use all the weapons it can produce to breach the body's own barrier against life-saving new parts: constantly refined surgical techniques, continued and improved use of dialysis, improved and simplified tests to insure the closest match with the recipient's own tissue, and the suppression of other rejection processes through new immunosuppressive agents and techniques, applied to both the donor organ and to the recipient.

Concurrently, there will be an ever-increasing need for healthy organs with which to replace diseased or worn ones. Already under study are tissue preservation techniques which will permit the storage of functional whole organs and diagnostic reagents until they are needed.

The Artificial Kidney

Artificial kidneys are mechanical devices that can be used to cleanse the blood when the natural kidneys fail. Until permanently functioning transplantation of healthy kidneys from living or dead donors becomes a practical reality, blood purification through repeated use of an artificial kidney (chronic hemodialysis) is the only hope for survival for the majority of such patients. While *some* patients in chronic kidney failure are being kept alive and productive through repeated treatment with the devices currently in use, *most* candidates for such treatment are unable to receive these benefits because of the extremely high cost and complexity of treatments.

Although artificial kidneys have been known for almost two decades and have been used in cases of poisoning or acute kidney failure, the use of these devices in any one patient has been limited in the past. Each time a patient

required the use of such a blood purifying apparatus, it was necessary to insert tubes into a major vein and a major artery to conduct the flow of blood from the patient through the artificial kidney and back into the patient's circulation. Each tube insertion often facilitated the onset of dangerous infections, and involved a new surgical procedure on a new pair of major blood vessels; thus, the number of times any one patient could be connected to an artificial kidney was limited.

About five years ago, an NIH grantee announced a successful innovation in the use of artificial kidneys aimed at permanent maintenance of patients with impaired or lost kidney function. His group, at the University of Washington in Seattle, had developed the use of permanently implanted, connected plastic tubes in an artery and vein of the forearm. This indwelling "Quinton-Scribner shunt" makes it possible to connect a patient repeatedly to artificial kidneys without special surgical procedures and without the use and ultimate sacrifice of a new set of blood vessels with each dialysis. Development of this shunt started a new era of hemodialysis in patients with permanently impaired kidney function.

During the last few years it has been shown that the repeated routine use of artificial kidneys in such patients on a regular schedule would permit the saving of lives which would be lost due to the otherwise fatal uremia. At the moment, however, using currently available techniques, the cost of hemodialysis both in terms of money and qualified manpower is extremely high, so that this life-saving treatment modality is, as yet, not available to all who might benefit from it.

The techniques and equipment involved still require improvement which must come about through strong research and development efforts. Authorities representing artificial kidney centers agree that improvements in hemodialysis must be based on additional knowledge of the nature of uremia. Such knowledge is as yet imperfect and must be developed side-by-side with efforts to improve artificial kidney apparatus and techniques, in order to assure maximal rehabilitation of patients maintained by chronic dialysis.

PERTINENT NATIONAL INSTITUTES OF HEALTH ACTIVITIES

For several years, intramural scientists have been working on the development of simpler, more efficient and more compact artificial kidneys, including one artificial kidney involving the use of activated carbon to absorb uremic wastes. These efforts have now advanced to a point where pilot models can be tested with laboratory animals and patients.

At the same time, the NIH has invested major funds in extramural support of research in hemodialysis with artificial kidneys and peritoneal dialysis (blood purification through washing of the abdominal cavity with special dialyzing solutions).

In the summer of 1965, Congress appropriated $3 million for the pursuit of a centrally directed program of research and development in chronic uremia, hemodialysis and artificial kidney development, utilizing predominantly a direct contract approach as well as increased research grant support. This program was located in the National Institute of Arthritis and Metabolic Diseases (NIAMD), the Institute which has major responsibility for urology and renal diseases research support.

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, 23 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 membrance 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 new program and are reviewing the scientific merit and feasibility of contract proposals.

It was also considered important that the new program be undertaken in close cooperation with the activities of the Kidney Disease Control Program of the Bureau of Disease Prevention and Environmental Control (BDPEC), PHS. 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 the closely interdigitating and interdependent nature of the NIH and BDPEC activities, both programs are in close and constant communication and work with a high degree of coopera-

tion. There is a constant exchange of essential data between both programs and the respective staffs of these programs, with particular emphasis on program planning activities. It is hoped that this close cooperation will assure a maximum of benefit and prompt developmental advances in the artificial kidney field.

OUTLINE OF 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.

PROBLEMS OF HIGHEST PRIORITY

The following are outstanding problems in dialysis toward which the new Artificial Kidney Program is directing immediate efforts:

1. Cannulas. The life and function of the permanently implanted cannulas are still limiting factors in successful dialysis.
2. Dialysis membranes. Though effective, the cellophane membranes currently in use may not be optimal. The possibility of using other, perhaps more selective membranes, must be explored.
3. Design of individual dialyzer units. Most dialyzers presently in use are cumbersome and costly to assemble and sterilize. There exists a dialyzer which utilizes a disposable dialysis-ultrafiltration "cartridge"; this cartridge is as yet too expensive for maintenance of chronic patients.
4. High requirement for professional personnel. This requirement is based on the medical nature of dialysis, but aggravated by problems 1, 2, and 3 above.
5. Lack of effectiveness data. No objective information has been obtained through well-controlled studies which permits a meaningful evaluation of the comparative effectiveness of the various dialysis methods and equipment currently in use. Such studies are facilitated by the existence of artificial kidney centers which provide the long-term patient care for this type of evaluation.
6. Undesirable symptoms frequently found in patients maintained by repeated dialysis:

   (*a*) Anemia. On the average, one or more blood transfusions are needed per month per patient maintained in dialysis—with the attendant high risk of transfusion hepatitis.

   (*b*) There is a significant incidence of peripheral neurological damage. This may be due to long-term effects of the semi-uremic state in surviving patients on repeated dialysis, or due to the dialysis procedure, *per se*.

   (*c*) Pseudo-gout, secondary hyperparathyroidism, skeletal demineralization, and calcium deposition in joints and in the tissues throughout the body. The most recent findings involve calcium deposition in the cornea of the eye. Simultaneously, there is a tendency to decalcification of bone with resultant fractures produced by minor stresses.

Problems 1 through 4 are primarily responsible for the current high cost of dialysis, which averages $10,000–$14,000 per year in patients maintained by hospital dialysis on a twice-weekly schedule.

IMMEDIATE PROGRAM ACTIVITIES

In brief the following are activities of primary concern of the Artificial Kidney Program.

1. Improvement of cannula materials, design and techniques so that current clotting and infection problems will be minimized. This involves redesign of cannula tips and bodies, development of a safer and simpler cannula coupling to the artificial kidney conduits, and the use of different cannula materials, including plastics permanently coated with anti-coagulants.
2. Development of improved or different membranes to permit a more selective and briefer dialysis. This involves the development and evaluation of tailor-made polymer membrances with controlled pore size and/or selective electrostatis properties, as well as mechanical modifications of the currently used cellulose sheeting, introduction of non-coagulating surface properties, and investigation of the metal binding characteristics of these new membranes.

3. More efficient, less cumbersome and less costly dialyzer design. This involves the improvement of new disposable dialysis-ultrafiltration units, development of more compact dialyzers requiring less blood for priming, overall redesign of machines to simplify and shorten assembly and sterilization, introduction to artificial kidney design of plastic materials with non-coagulating surfaces, and expansion of two new concepts in artificial kidney dialysis; (a) "hollow fiber" kidneys, and (b) "diafiltration"—blood purification primarily through ultrafiltration, followed by artificial reconstitution of the filtrable blood solutes.

4. Improvement of technical and hardware efficiency and safety of large hospital dialysis centers and of home dialysis units. In hospital centers, this involves development of improved automatic central fluid delivery systems, and fail-safe monitoring systems for all aspects of dialysis (blood leakage, temperature, ionic concentrations of fluids). In home dialysis units, this will also involve inclusion of a fail-safe mechanism in the dialyzing equipment in the event of accidental blood leakage—to permit unattended dialysis at night when patient and family are asleep.

5. A systems analysis of the entire present chronic dialysis effort and of its methodologies and equipment. This includes 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 includes a registry of all patients presently maintained with the aid of artificial kidneys or peritoneal dialysis, which will permit a truly comparative evaluation of the effectiveness of equipment involved and various methodologies of treatment. This overall systems analysis will continue as a longitudinal study of these patients and will be undertaken as a cooperative effort with the community service programs in dialysis of the Kidney Disease Control Program, BDPEC, 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.

ACTIVITIES TO DATE

The Artificial Kidney-Chronic Uremia Program was mounted in record time with the activation of 24 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 major problems. These projects involve development of improved blood cannulas; 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 a prototype for a portable artificial kidney; and many other related projects.

The portion of the program which is funded by extramural research grants complements closely the contract program described above, but is oriented more toward elucidation of clinical and fundamental biological problems related to the treatment of chronic uremia rather than toward hardware development. It involves studies on urea metabolism in uremic patients undergoing chronic dialysis; the undesirable side effects of chronic dialysis; the effectiveness of peritoneal dialysis in uremic patients; other novel approaches to blood purification in chronic kidney failure such as dialysis of a surgically relocated, isolated intestinal loop, lymph dialysis and dialysis in the home; and the nature of the biochemical defects in advanced uremia.

Thirty-two new research and development contract proposals have already been received in fiscal year 1967, and a substantial portion is in the process of being activated. These proposals embody unique, new approaches to artificial kidney methodology such as diafiltration (a novel concept in artificial kidney design); 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.

Periodic optimistic stories in the lay press notwithstanding, the ultimate cheap, simple, efficient and safe artificial kidney for home use does not yet exist, nor does it loom in the immediate future. The program as outlined above is expected to close existing gaps systematically and to deal with treatment complications. Simultaneously, it introduces new engineering developments into the maintenance treatment of uremic patients and, hopefully, will lead toward both better hardware and improved patient rehabilitation.

Kidney Disease Research

This past year, NIH-supported scientists have reported on a host of findings shedding light on several diseases involving the kidneys in order to better understand and hopefully prevent lesions that produce chronic renal failure. Some of these are uremia, cystinuria, glomerulonephritis, chronic pyelonephritis, the nephrotic syndrome, and hypertensive kidney disease.

UREMIA

A low-protein intake is considered useful in the treatment of some patients with uremia because the failing kidney is no longer able to handle the excretion of urea and other nitrogen-containing products of protein metabolism in the body. The accumulation of these nitrogeneous substances is believed to be responsible for some of the symptoms of uremia.

A group of Italian grantees has noted that chronic malnutrition is often present in patients with chronic renal failure. Severe protein depletion is often present because of breakdown of body protein resulting from dietary protein restriction, a poor food intake because of lack of appetite, and in some instances urinary protein losses as a result of kidney damage. Tissue wastage and resorption of bone matrix are reported to be frequent results of this severe protein depletion. Their dietary approach is aimed at restoring nitrogen balance without overloading the kidney's impaired nitrogen-excretion capabilities. They have employed diets containing from 18–25 grams of protein daily. If one of these diets fails to improve the patient's clinical condition, he is placed on a diet containing eight essential amino acids in amounts comparable to 8.5 grams of protein daily. These diets usually decreased blood nitrogen levels and produced clinical improvement, especially if a positive nitrogen balance could be maintained. Surprisingly, positive nitrogen balance was observed most frequently in patients on the essential amino-acid diet, which contained less total nitrogen than any of the others. Biochemical studies, using labelled urea in uremic patients on the low-nitrogen diets, indicated that some of the urea was being actively used in the synthesis of amino acids and protein. This might help to explain both the decreased azotemia and the improved clinical status of patients maintained on these diets.

In two separate and unrelated studies this past year, scientists have made significant contributions toward identifying and characterizing the toxic factors in uremia, essential to a better understanding of uremia and to improving hemodialysis appartus and techniques.

Treatment of uremic patients with the artificial kidney or with peritioneal dialysis usually results in clinical improvement, suggesting that the small molecules removed by dialysis contribute to the symptoms of uremia.

Recent studies have suggested that catabolism of aromatic amino acids may lead to accumulation in the blood of intermediate products which may play a role in development of the toxicity of uremia. Now it has been shown that blood levels of aromatic amines (degradation products of aromatic amino acids) are markedly elevated in uremic patients, that these high levels are correlated with blood urea nitrogen levels, and that they may be reduced significantly by hemodialysis with an artifical kidney. These findings suggest that aromatic amines may plan an important role in the toxicity of uremia.

Another investigator has demonstrated that protein synthesis, as measured by an *in vitro* amino acid incorporation system, is markedly impaired by two specific organic compounds isolated from hemodialysis fluid of uremic patients. It is suggested that this assay system may be of value in determining the toxic components present in uremic patients.

CYSTINURIA

Cystinuria, a disease characterized by urinary excretion of large amounts of cystine and other amino acids, and by formation of cystine stones in the urinary tract, is attributed to a hereditary transport defect in the kidneys. It has been suggested that cystinuria is due to more than one single inherited disease process, however, and evidence was recently obtained of an intestinal as well as a renal transport defect in this disorder. The reported findings indicate that cystinuria encompasses at least three biochemically and genetically distinct diseases.

In cystinuria, the kidneys excrete excess amounts of cystine. Since cystine is relatively insoluble, cystine crystals may be produced in the urine and may accumulate in the kidneys, frequently leading to the development of kidney stones. Conventional therapy, including increased fluid intake, alkalinization of the urine, and dietary restriction of methionine (a metabolic precursor of cystine), is not always effective.

It is known that penicillamine, a degradation product of penicillin, can markedly reduce urinary cystine excretion and prevent new stone formation by reacting with cystine to form the more soluble penicillamine-cystine. Recent work, both in Bethesda and by grantee scientists, now has shown that prolonged penicillamine therapy sharply reduces the size of existing cystine stones in the kidney and eventually dissolves them completely, without serious side effects.

GLOMERULONEPHRITIS

NIH grantees have developed a new vaccine that may help prevent streptococcal infections, which frequently lead to rheumatic fever in children and may be the basis of glomerulonephritis in both adults and children. Although the majority of patients with glomerulonephritis recover, a significant number enter a chronic stage of kidney function impairment that ultimately progresses to chronic kidney failure.

The investigators have found their new vaccine to be safe and effective in extensive tests with mice, rabbits, and guinea pigs. In tests on nearly 50 adults, it has led to no serious reactions and has greatly increased the levels of antibodies against streptococcus organisms. Only further testing, particularly in children, will determine the effectiveness of the new vaccine in preventing streptococcal infections under ordinary conditions.

The investigators are working at present toward development of a vaccine that will be effective against the five or six types of streptococcus organisms that cause most infections in urban populations.

CHRONIC PYELONEPHRITIS

Chronic pyelonephritis, a slowly progressive kidney disease, is believed to result from the scarring effects of a pre-existing bacterial infection, as well as from persisting and recurring bacterial infections. The disorder apparently occurs more frequently in diabetic patients than in other groups, but there is little unanimity of opinion as to the actual frequency of the disease in diabetic and in nondiabetic groups.

Histologic and bacteriologic studies by an NIH grantee now have shown that there is essentially no correlation between the presence of positive urine cultures, positive renal tissue cultures, and the histologic diagnosis of chronic pyelonephritis in juvenile diabetic patients. These findings suggest that factors other than the continued presence of bacteria in the kidney may play a role in the pathogenesis of chronic pyelonephritis.

NEPHROTIC SYNDROME

A long-term NIH-supported study of patients with the nephrotic syndrome has revealed that such individuals have an incidence of cancer ten times that of comparable population groups. This finding suggests a more than coincidental relationship between these diseases and indicates a need for careful and repeated screening of nephrotic patients for malignancies.

Of 101 patients with idiopathic nephrosis studied between 1953 and 1962, 11 (or 10.9 percent) were found to have malignant neoplasms anywhere in the body. The incidence of cancer in comparable population groups, paired according to age and sex, was one percent. None of the 11 patients had received anti-

cancer therapy which might produce nephrosis. Renal amyloid involvement and renal vein thrombosis were also ruled out.

It is known that patients with neoplastic disease frequently develop antibody directed against their lesions, and there is evidence to indicate that membranous glomerulonephritis and lipoid nephrosis are immunologic diseases. The high incidence of cancer observed in nephrotic patients in this study suggests a relationship between these diseases; materials released from neoplasms may act as antigens which subsequently cause the production of antigen-antibody complexes capable of inducing the characteristic renal lesions of the nephrotic syndrome.

HYPERTENSIVE KIDNEY DISEASE

Renal failure is a common cause of death in patients suffering from malignant hypertension. Recently, however, unequivocal evidence has been developed to show that modern blood pressure-lowering drugs are saving many lives by preventing renal damage as well as other fatal consequences of essential and malignant hypertension.

The known incidence of hypertension secondary to primary kidney disease and renovascular disease has increased progressively as improved methods have been devised for diagnosing these ailments and for determining their various (and variable) effects in the body.

In renovascular hypertension, for example, the improved diagnostic acumen of physicians has enabled them to: (1) determine the location and extent of blood clots or atherosclerotic deposits obstructing renal blood vessels; (2) measure the effects of such obstructions on renal function in one or both kidneys; (3) choose that method of medical and/or surgical treatment most likely to benefit the patient; and (4) assess the results of therapy. Surgical reconstruction or bypass of affected vessels will often cure renovascular hypertension if the obstructions to bloodflow are confined to surgically accessible sites and if they have caused no permanent damage to the kidney. Otherwise, removal of one kidney will be required to control the hypertension resulting from kidney damage. If only one kidney is affected, prompt and accurate diagnosis followed by repair or removal of that kidney can often prevent hypertensive damage to the other kidney.

NEW DIAGNOSTIC METHODS

An improved method of percutaneous renal biopsy, whereby a sample of kidney tissue for analysis is obtained with a special needle inserted through the patient's back, utilizes television-monitored fluoroscopic guidance of the needle to avoid potentially hazardous "blind" probing and to insure that tissue suitable for diagnosis is obtained. The scientists, who introduced the standard technique in 1952, state that their improved technique is now the method of choice for biopsy of the kidney.

Differentiating between acute and chronic renal failure in a uremic patient is often extremely difficult. This distinction is a very important one for the physician to make, however, since most medical centers are prepared to dialyze temporarily the patient with acute renal failure in the hope of eventual recovery, whereas only limited facilities exist for the chronic intermittent dialysis of patients with end-stage renal disease.

A grantee scientist has postulated that measuring the creatinine content of fingernail and toenail clippings would permit an estimation of the duration of renal failure and thus provide a basis for separating acute and chronic uremia patients. His reasoning was based on the premise that the creatinine content of the clipped free edge of the nail, which was formed many months earlier, would reflect blood creatinine concentration (hence the presence or absence of uremia) which was present at that time. Results of creatinine analyses of nail clippings from normal persons and patients with renal failure of varying degree and duration bear out his theory.

He found that patients with acute renal failure had normal nail creatinine concentrations, whereas those with chronic renal failure had elevated levels that correlated with the blood creatinine levels present several months before. Patients with chronic renal failure who regained normal kidney function after successful renal homotransplantation continued to have elevated nail creatinine levels until several months after blood levels returned to normal.

SCIENTIFIC COMMUNICATION ACTIVITIES

In a major effort to meet the scientific communications problem in kidney disorders, and to acquaint the professional community with kidney research, the NIAMD has begun a vigorous program to expedite communication of pertinent laboratory and clinical findings. This past year, the Institute began publication of a new current-awareness bibliography on chronic kidney failure and on artificial kidney and dialysis methods covering relevant scientific papers from throughout the world. The publication, *Kidney Failure and Artificial Kidney Bibliography*, has been made available to interested investigators in this field and has been received enthusiastically. It was prepared to explore the possible utility, content and format of a new quarterly bibliography dealing with research and development in the area of chronic kidney failure and improvement of artificial kidney and dialysis methods.

Also developed this past year were an exhibit and an accompanying brochure to provide general information for present and prospective participants in the Artificial Kidney-Chronic Uremia Program. Both exhibit and brochure describe areas of emphasis in this program and the procedures and methods utilized for supporting research, applied research and development.

The Third International Congress of Nephrology was held this past year in Washington, D.C., and was sponsored primarily by the National Heart Institute and the National Institute of Arthritis and Metabolic Diseases. Principal objective of the Congress was to promote the international exchange of scientific information on activities in the basic and clinical sciences relating to the kidney. Over 2,000 scientists from some 44 countries attended the Congress.

KIDNEY DISEASE: SUMMARY

Research conducted or supported by the National Institute of Arthritis and Metabolic Diseases, the National Institute of Allergy and Infectious Diseases and the National Heart Institute has added considerably to the understanding and treatment of chronic kidney disease. Latest morbidity and mortality figures due to kidney diseases reflect the acute need for continuing and intensifying research efforts in this area.

Significant advances have been made in research on the prevention, diagnosis and treatment of the varying disease processes which attack the kidneys. Investigators delineating the basic abnormalities of the chronic uremic state have contributed considerably to our understanding of the condition.

Increased understanding of the fundamental disease processes has brought with it a significant improvement in treatment methods. Kidney transplantation at present shows promise of becoming a major treatment modality for chronic kidney failure. Immunological host-transplant incompatibility remains the major difficulty to successful kidney transplantation today. Steps are being taken to overcome this problem through a tissue-typing program (matching cell antigens of ricipient and donor) and through studies for more effective and less toxic agents to control the immune response.

Until kidney transplantation becomes a practical reality, blood purification through an artificial kidney (chronic hemodialysis) is the only hope for survival for the majority of patients with chronic kidney disease. Moreover, a number of patients are unable to receive or successfully maintain a kidney graft due to physical, immunological, or financial reasons. Major efforts have been made in the direction of developing simpler, more efficient, more compact, and less costly artificial kidneys, allowing for the effective treatment of an increasing number of patients.

As an alternative or adjunctive method of therapy for patients with chronic kidney failure, especially those less seriously impaired, the use of a special, low-protein diet has shown considerable promise.

Investigations such as those outlined above have added much to our ability to cope with and prevent kidney failure. They have also indicated areas for new research efforts in order that more widespread and more permanent control of this group of diseases may be accomplished.

SUMMARY OF BUDGET REQUEST FOR ARTHRITIS AND METABOLIC DISEASES

Mr. FLOOD. Your adjusted appropriation for 1967 is $134,695,000 and your request for 1968 is $143,954,000. That is an increase of $9,259,000.

RESERVE

This is the largest so-called "Unobligated balance, reserve" we have come across so far in NIH, $1,724,000. I think there is a bigger one we will come to later, but this is the biggest we have seen thus far. Why are you so honored in view of all these nine pages you have just read to us?

Mr. NEIL. Mr. Chairman, could I leap into the fray here?

Mr. FLOOD. Sure. Who are you?

Mr. NEIL. I am filling in for Mr. Cardwell. I am Henry Neil, Director of the Budget Division in the Office of the Secretary.

You will recall Mr. Kelly's presentation at the outset of the hearings on the cutback or savings program for 1967. Among other things that he identified as being part of the savings program was the placing in reserve those amounts where the estimate of requirements had changed from what it was when we presented the budget last year. Most of this large reserve to which you refer in this Institute falls in that category.

Mr. FLOOD. I remember Mr. Kelly's presentation very well but here you have $1,724,000 in reserve from the Institute's appropriation. Specifically, why?

Mr. NEIL. Last year when we presented the budget we made an estimate based on continuing research projects which had been approved in prior years.

Mr. FLOOD. That is right.

Mr. NEIL. This year our estimate for supporting continuing research projects for this Institute is less than had been estimated in last year's budget.

Mr. FLOOD. This was a good estimate that went wrong someplace?

Dr. SHANNON. Mr. Chairman, the estimate that appeared in last year's budget that came before this committee consisted of three elements: (1) funds for wholly new grants; (2) for grants committed beyond the immediate budget, for which we had committed continuations; and (3) uncommitted continuations.

In constructing a budget, the Congress then looked at our committed continuations and made provision for a certain proportion of new starts and a certain proportion of continuations of research projects that had already been established but for whose continuation there was no commitment. The committed continuations were calculated in September of 1965. In the fall of 1967 it was shown that savings of one sort or another had taken place and that the continuation needs were substantially below the estimate of the year before. In constructing the 1967 operational budget a reserve to the extent of this difference was taken. So one should not discuss program requirements but program elements.

Mr. FLOOD. You mean you saved us money?

Dr. SHANNON. No, sir. The estimate your committee saw last spring was an estimate for continuation made last fall.

Mr. FLOOD. Yes, but we got them from you.

Dr. SHANNON. This is correct, sir. I may say this is never a precise figure. For three of our Institutes, the estimates were high—National Institute of Arthritis and Metabolic Diseases, National Institute of Neurological Diseases and Blindness, and National Institute of Child Health and Human Development. The others were on the low side.

This is one of the results of making estimates based on the three elements I mentioned. This reduction was taken by the Department as a savings program because it would hurt the program less than if taken in other areas. This is the way the Bureau of the Budget elected to do it—as being less harmful to the program.

Mr. FLOOD. The margin for error. Well, that is a handy tool to have around.

Dr. SHANNON. Mr. Flood, you must realize that the projections are made a year apart. Many factors enter into it. This type of projection represents about 10 percent of the total activity. Some estimates are high and some are low. If we could present an estimate for the total activity, you would find it rather precise, but when you break it down into 13 individual accounts, then the error in each account is proportionately high.

RHEUMATOID ARTHRITIS

Mr. FLOOD. Last year we told you—and, of course, you mentioned it yourself—we thought a great deal more should be done about rheumatoid arthritis. Can you bring us up to date on that?

Dr. WHEDON. I shall be happy to, Mr. Chairman. We have really made considerable progress during the past year and it has been an accumulative progress which had a running start from a few years back when we began to be aware of the importance of immunity factors in this disease, with the real likelihood that the defense mechanisms of the body, so-called immunity processes, were not behaving properly and were tending to become manifest against some proteins of the body's own manufacture. As a result of this, we were able to determine the rheumatoid factor in the blood, which has been useful particularly in identifying patients with rheumatoid arthritis and it has also helped to some extent in determining the effects of treatment. The importance of this immunity problem has been intensified a little over a year ago by the discovery of the probable importance of the unusual microorganisms I mentioned in my statement. The viruses and the mycoplasmas, which are very small, smaller than bacteria. I think there are various other bits of information which indicate the importance of this immunity process. I mentioned in my opening statement the production of so-called adjuvant arthritis in mice and the fact that this could be prevented if the mice were injected with an antilymphocyte serum. The mice were then prevented from developing polyarthritis by suppressing the processes of immunity. This gives us hope that within a reasonable period of time we can develop an effective form of therapy in rheumatoid arthritis and other diseases associated with faulty immune mechanisms.

I believe I mentioned as a preliminary development this year the use of a chemical which would act in suppressing the immunity process. This fits the same general picture in such a way that we are expecting to place greater emphasis on these drugs.

Mr. FLOOD. If you suppress that in the body for this purpose you have suppressed it for all purposes; have you not?

Dr. WHEDON. Mr. Chairman, this is a very sensible question, and it highlights the extreme care with which a therapeutic or clinical management project of this type must be undertaken, because the exact dosage of these compounds must be watched very closely, as

well as the condition of the patient himself, and the various elements in the blood which will indicate the patient's ability to respond to other types of invasions.

Mr. FLOOD. It would be a very delicate balance in some cases?

Dr. WHEDON. Yes, and that is why these studies are not a matter of one, two, three. They have to be done very carefully.

ARTIFICIAL KIDNEY

Mr. FLOOD. You spent some time in your original statement telling us about your progress in the development of the artificial kidney. As you know, this committee has made quite a point of stepping up activity in this area. Do you have anything to add to what you said in your statement?

Dr. WHEDON. I shall be glad to supply additional information.

Mr. FLOOD. What else should we know other than what you have told us? What is new within the last year?

Dr. WHEDON. I think it might be worth placing in the record, Mr. Chairman, that we feel we have made rather rapid and solid progress in this program. It was begun only a year ago with a little over $1 million. We are now at a level of $4.3 million. The main emphasis here is the awarding of contracts to conduct a series of developmental approaches to improved hardware and improved techniques with the artificial kidney. I simply would like the record to show that we feel we are proceeding on a very sound basis along these lines. We are getting at some of the very obvious problems that have to be managed. The problem of the cannula—that is the device by which the physician has access to the circulation each time he has to make an artificial kidney treatment. This cannula is a problem because since it is open and susceptible to the air, infection could take place. Also there is a prospect of clotting in the cannula after a period of time, after which it has to be replaced.

One of the members of the committee earlier today was asking about the interest of the engineering community in biomedical problems, and we have undertaken a very active pursuit of their interest in this regard. Chemists, for example, are coming up with membrane surfaces which will prevent clotting, and they are attempting to coat the cannula and other surfaces with nonclotting materials.

I would like to add further, though, that this is not a project that is near completion. There still remain some very difficult problems. We know that with this kidney treatment we can remove many of the substances which make the patient ill, but with the present cellophane membrane we may not remove all of the right toxins. Some serious toxin may still remain, and we are also removing some natural elements which should remain in the body. I refer particularly to calcium, for example. There tends to be a wasting and thinning of the bones of patients who are on this repeated, continuing chronic kidney dialysis treatment. So a substantial part of our future plans consists of awarding contracts for research grants to see what actually goes on in uremia which brings about the deleterious effects and eventually the death of the patient.

CLARIFICATION OF JUSTIFICATION MATERIAL

Mr. FLOOD. You know, the justifications that you send up to us are supposed to enlighten the committee. At least that is the purpose, as I understand it. Sometimes they do and sometimes they do not. In some instances I have the impression you want to be more erudite than informative when you engage in these semantics. Look at the bottom of page 133. I wonder if you ever saw this before. This is exhibit A. If whatever you say there is significant, the committee would like to know what it means. This is a classic example of what I am pointing out.

Dr. WHEDON. First of all let me assure you that to confuse is not our intention; to inform is indeed our purpose.

Mr. FLOOD. If there is any significance in this exercise of semantics we would like to know what it is.

Dr. WHEDON. The paragraph I am looking at, Mr. Chairman, has to do with rheumatoid arthritis and has to do with a "distinctive multinucleated synovial giant cell in rheumatoid arthritis." The word "distinctive" here means it is unique. The word "multinucleated" as related to a cell means a cell that has more than one nucleus. Most cells have only one nucleus. In certain cells, particularly those related to protection against infection, there may be more than one nucleus. The most frequently found white blood cell is called a "poly" because of its polynuclear structure. "Synovial" refers to joints. In this situation there have been found some unusually immunity-related cells called giant cells which have many nuclei, and the significance is that these cells were found in joint fluid in nine out of 19 patients with rheumatoid arthritis and not in any patients without rheumatoid arthritis. It means that if you have a patient with swelling and pain in the joints and the doctor is in doubt as to whether this came about because of trauma or a fall or whether a person has gout or whether it is rheumatoid arthritis, if the doctor will take a needle and carefully take some fluid from the joint, if he finds multinucleated synovial giant cells he knows the patient has rheumatoid arthritis.

CIRRHOSIS OF THE LIVER

Mr. FLOOD. You told us something about diabetes and peptic ulcers. What about cirrhosis of the liver? I have heard it said cirrhosis of the liver is prevalent in people who drink too much alcohol. I have also heard it is not the drinking of the alcohol at all that produces cirrhosis of the liver; it is the fact they do not eat a balanced diet. It is a question of lack of proper food, or is it the alcohol, or a combination of both.

Dr. WHEDON. We have shared for a good many years, the delusion that you have described, and it has only been in the last year that studies have been developed which show that proper feeding of animals in which alcohol was administered did not protect the liver as we thought it should.

Mr. FLOOD. Does it appear to be a direct effect of alcohol?

Dr. WHEDON. It appears to be a direct effect of the alcohol. I should add that this is not to discourage eating. In other words, there may also be a nutritional protective factor which is important in addition to some toxin which is in the alcohol itself.

Mr. FLOOD. But you are making the point that more or less the alcohol is a direct cause of this condition?

Dr. WHEDON. That is correct, and that just proper eating alone will not fully protect against the possibility of the development of cirrhosis of the liver.

I should add that fortunately not everyone who drinks develops cirrhosis of the liver so that some of these factors may interact with one another.

Mr. FLOOD. It is the result of excessive drinking alcohol over a long period of time?

Dr. WHEDON. Usually, yes, over a prolonged period of time.

Mr. FLOOD. Mr. Laird.

GENETIC COUNSELING

Mr. LAIRD. Dr. Whedon, we are learning more and more about genetics and, from time to time, we hear about the need for genetic counseling. Would you like to comment on that?

Dr. WHEDON. Mr. Laird, that is a very exciting question to me because it indicates your astute awareness of the progress we are making in understanding life's processes. And although I hesitate to get into this tumultuous subject, we are beginning to reach a point where we know enough about the biochemical processes of the body and the processes by which various enzymes are made and reproduced and passed on from generation to generation, that we will be able to provide some very expert genetic counseling to a man and a woman who wish to marry and have children. I hasten to add that it will never be within our province to lay down any rules or regulations as to what is to be done, but I think we will have the opportunity, within a very few years, of being able to carry out certain tests on individuals and tell them quite accurately what the possibilities are that they will have in one or another of their children this or that rather serious disease, then they would have free choice, I would trust, as to what they will do with this information.

Mr. LAIRD. Do you think that is apt to make a better life for them?

Dr. WHEDON. I can think of one very practical way in which this might make a better life. If it could enable a couple possessed of the knowledge that they were highly likely to have a child with severe mental retardation to make their own choice that they would rather not have children, then they will have avoided heartbreak and untold expense by having avoided the problem.

Dr. SHANNON. Of course, it has practical applications now. It permits the alert physician to take steps, at the very first sign of pregnancy, to protect the child. So I do not think this is a wholly negative type of information. I would hope, that as we gain knowledge of the hazards, we will concurrently develop a capability to deal with the hazards.

I personally feel that we are unduly preoccupied with disease and death and too little occupied with the quality of life. I think these questions should be discussed now so that when more powerful biological tools become available to us we will know how to use them.

Dr. WHEDON. I would like to give one example of practical application now and that is the Rh factor with which I think eveyone is familiar. If a husband and wife know there is a potential for a prob-

lem in their children, the physician can—first of all, I should supply for background that usually the very serious manifestation of a problem in this area does not occur with the first pregnancy. It usually takes two or three or possibly four pregnancies before there is a manifestation of the disease, but the physician can begin protecting the child by immediate testing of the infant.

Mr. LAIRD. Are you not changing the blood in the child now before birth?

Dr. WHEDON. No. The usual procedure is exchange transfusions after delivery. The test is made of the infant's blood, actually from the umbilical cord, right at birth. If it is apparent that the child does have a positive Rh factor and anti-Rh antibodies, as soon as the first sign of hemolysis appears, a complete exchange of blood can be effected.

Mr. LAIRD. Can they not do that before birth?

Dr. SHANNON. They are testing for the condition before birth.

Mr. LAIRD. I thought in Canada they were doing that.

Dr. SHANNON. On an experimental basis, it is being done to a very limited extent. I would not say that it is a common practice today.

Mr. LAIRD. But it is being done, it is not?

Dr. SHANNON. Yes, on an experimental basis.

Mr. LAIRD. It was my understanding that they had been successful, I think in Montreal, where they have been doing this.

Dr. SHANNON. That is correct.

HISTORY OF BUDGET REQUEST

Mr. LAIRD. Dr. Whedon, in your request to the Public Health Service you asked for $159,659,000. This was reduced by the Public Health Service to $156,889,000. What was included in this approximately $3 million reduction, what items?

Dr. WHEDON. The principal reduction was in research grants, in which there was a reduction of about $1.5 million.

Mr. LAIRD. About half of it, then, was in research grants?

Dr. WHEDON. Yes. Another $400,000 was in fellowships. There was also a $707,000 reduction in collaborative research and development and field studies.

Mr. LAIRD. Then in the submission to the Bureau of the Budget there was a reduction of $3.7 million. What was in that reduction?

Dr. WHEDON. Well, there were some complicated changes at that stage, but the major change was a reduction of $4.1 million in research grants. An adjustment was made in the collaborative research account recognizing the importance of the artificial kidney program whereby $700,000 was returned.

Mr. LAIRD. They added to the artificial kidney program $700,000 more than you requested?

Dr. WHEDON. No. They restored what had been taken away in the earlier stage.

Mr. LAIRD. At the Public Health level?

Dr. WHEDON. Yes.

Mr. LAIRD. What happened at the next stage—the President's budget—where there was a reduction of $10 million? Was any of it involved in the artificial kidney?

Dr. WHEDON. No.

Mr. LAIRD. What is the total program on the artificial kidney?

Mr. BAYLIS. The total program on the artificial kidney is $6.8 million for fiscal 1968 and $4.3 million for 1967.

Mr. LAIRD. The $10 million reduction at the President's level is mainly attributed to research grants?

Dr. WHEDON. Yes.

Mr. LAIRD. And that amounts to how much?

Dr. WHEDON. The reduction between the Department and the President's budget was $7,110,000.

Dr. SHANNON. And $2,294,000 in training grants.

Dr. WHEDON. That is correct.

ESTIMATED UNFUNDED RESEARCH GRANTS IN 1968

Mr. LAIRD. What is your estimate of the resarch grant application that will be submitted to the Institute during fiscal year 1968, in cluding those that are unfunded at the present time but approved?

Dr. WHEDON. I may not be able to answer that directly, Mr. Laird, but we anticipate that during fiscal year 1968 we will have grants approved by a study section which will be in excess of our funds to pay by $8 million. The value of approved but unfundable research grants in fiscal year 1967 is now estimated at $6.7 million.

Mr. LAIRD. These are study section approved?

Dr. WHEDON. Approved as being meritorious which the Advisory Council would like to consider as to relevance to our program but they would hardly take time to consider because of the lack of funds to support it to that extent.

KIDNEY PROGRAM

Mr. LAIRD. Under the kidney program how many research and development contracts have you made in fiscal year 1967?

Mr. BAYLIS. About 24 contracts, sir, a little under $2 million in fiscal year 1966. We estimate full use of the $4.3 million in fiscal year 1967 with the number of additional contracts, roughly about 23, I believe, just having completed our final review.

Dr. WHEDON. We have now 29 contracts active and we have just approved in meetings which have just taken place an additional 18 contracts and expect to have 47 active by July of this year.

Mr. LAIRD. What is the average of these contracts in dollars, approximately?

Dr. WHEDON. They range, if I may try that first, all the way from about $12,000 to about $400,000 and I would estimate the average is $95,000.

Mr. LAIRD. That is mostly equipment costs.

Dr. WHEDON. It is mostly for artificial kidney fabrication, and for improvement of materials, design and techniques.

Dr. SHANNON. The purpose is to purchase information. These are industrial contracts that are part and parcel of the program aimed at solving quite specific operational problems.

Mr. LAIRD. What do they use the money for?

Dr. WHEDON. For the development of better techniques. This is not for the purchase of scientific equipment for routine use.

Mr. LAIRD. You are reimbursing them, are you not, for equipment?

Dr. WHEDON. For development of new artificial kidney equipment, for developing better design, for production and testing of membranes for dialysis of blood which have never been used before. The major item in these contracts is for calories.

Mr. LAIRD. You are getting the information to improve the program which is funded under the Public Health Service chronic disease program?

Dr. WHEDON. That is correct.

Mr. LAIRD. You work closely with them so they have the benefit of all of this new information.

Dr. WHEDON. We have representatives that attend each other's meetings in which we review the various contracts and proposals in each other's programs. I would like to add that we feel that it is very important for us in making substantive progress in dealing with this problem that we know everything there is to know about the some 600 patients that are thus far on chronic dialysis treatment. This very careful review and analysis of the types of patients, the type of disease, the kind of artificial kidneys they have been on, the frequency of dialysis, and so on, has been initiated in part by the Chronic Disease Division, now called the National Center for Chronic Disease Control, and will now be taken over by a contract under our support. We are doing this, I might say, not only in conjunction with the important other Divisions of the Public Health Service, but with the very active cooperation of the Veterans' Administration which has a number of active centers under their own sponsorship.

THE HOME DIALYZER

Mr. LAIRD. Who developed the home dialyzer? Did you develop that in this area, or was this developed in the chronic disease area? They have contracts too.

Dr. WHEDON. Yes; but the purpose of their contracts is the support of demonstration centers for the care of patients, and what they are studying are better methods of management of centers and management of personnel, common use of equipment and that sort of thing."

Mr. LAIRD. You work well together.

Dr. WHEDON. Yes.

Mr. LAIRD. It looks to be as though it is separate in the justification.

Dr. WHEDON. It is separate in the justification.

Mr. LAIRD. Who developed the home dialyzer?

Dr. WHEDON. This was developed under our aegis and support because our main function is to develop better equipment.

Dr. SHANNON. May I clarify the relationship, Mr. Laird? Earlier it was pointed out by Dr. Whedon that by NIAMD support they had improved cannulas, improved dialysis membranes and improved packaging of the whole think that made possible a simpler and more effective dialysis unit. Actually they can do dialysis in substantially less time than the present, more cumbersome, mechanism does.

Mr. LAIRD. And at less cost.

Dr. SHANNON. Yes. They are having prototypes of these made. They will put them out on test and if they operate as effectively as one would expect, then, presumably, they will replace the on-going units in the chronic disease program. They are trying, through operational research, to reduce this to a practical technique. In other words,

we will not carry it beyond the demonstration stage. We will show that the prototype works and has these limitations and we will turn over the improved technique. There must be a very intimate interplay but there are very sharp boundaries between the two programs as to which of the two partners does what.

Mr. LAIRD. That is all I have.

Mr. FLOOD. Mr. Smith?

ALLOPURINOL

Mr. SMITH. Doctor, in your recent report on arthritis you said that one of the important types of acute, extremely painful, sometimes chronic destructive arthritis is gout. During the past year, FDA approved a new drug, Allopurinol. Did NIH play any part in this role?

Dr. WHEDON. I believe the drug itself was produced by a pharmaceutical company but we played a very active role in support of studies with the compound and were able to determine its actual effect on patients with gout, that it actually suppresses the formation of uric acid.

Mr. SMITH. You did some important basic research?

Dr. WHEDON. We contributed to the understanding of its mechanism of action.

Mr. SMITH. Is the drug patented?

Dr. WHEDON. I believe it is.

Mr. SMITH. Does the company own the patent?

Dr. WHEDON. I may be somewhat hesitant in replying because I am not certain of the answer, but I strongly suspect the compound had already been developed as a compound by a pharmaceutical house and by some knowledge of its composition, other actions, et cetera, it was thought that it was possible that it would be applicable to this problem.

Mr. SMITH. Will you place in the record an explanation of what the circumstances really are, whether or not it is patented, and if so, why it was not something that was in the public domain.

Dr. WHEDON. I shall be happy to.

(The information follows:)

An entire group of chemical compounds related to allopurinol, and including it, had been studied in the past for several years in connection with their potential use as anti-cancer compounds. These studies were undertaken both under industrial auspices and for the Southeastern Cancer Chemotherapy Cooperative Study Group with NIH funds (primarily from the National Cancer Institute). Several compounds of this series were found to be inhibitors of xanthine oxidase. In this group, 4-hydroxypyrazolopyrimidine (HPP, and as it is now known, allopurinol) turned out to be ineffective as an anti-cancer compound but was demonstrated by Dr. Hitchings of Burroughs Wellcome (a drug firm active both in England, United States, and Canada) to be a powerful inhibitor of xanthine oxidase *in vitro*. This, in turn, gave promise of suppression of uric acid production, and Doctors Rundles and Wyngaarden of Duke University School of Medicine were asked to investigate the clinical aspects of the drug's suppression of uric acid production in patients with gout.

HPP (or as it is now known, allopurinol) was discovered in a Burroughs Wellcome laboratory in 1956. Burroughs Wellcome and Company filed a patent application for this drug in 1956—several years before its anti-uric acid properties became known, which was in 1963. One patent on the drug is about to be issued in the United States and another one is still pending. Patents have been issued to Burroughs subsidiaries in England and Canada in 1956 and 1957, respectively.

Cystic Fibrosis

Mr. Casey. Doctor, what are we doing on the cystic fibrosis mentioned in your statement? I think you stated you might submit a more detailed report later. I thought you might give us the benefit of something today, if you could.

Dr. Whedon. We have a special report prepared which we shall be happy to submit as part of the testimony.

(The Special Report Follows:)

Special Report: Cystic Fibrosis

Cystic Fibrosis (CF) is an inherited generalized metabolic disorder characterized by an abnormality in the products of all bodily glands which secret fluid to external body surfaces. (By medical definition the gastro-intestinal and respiratory mucosa represent such external body surfaces.) These glands secrete two major types of fluid—watery sweat produced primarily by the glands of the skin, and mucus fluid intended to lubricate the bronchioles of the lung and the gastrointestinal tract. The abnormalities which occur in both these types of secretions are responsible for the clinical symptoms and signs observed which have been recognized as the distinct disease entity, cystic fibrosis, since 1938.

The basic metabolic disorder of exocrine secretion results in three principal clinical problems. First, and least disabling, is the production of sweat with a high salt content. The unique composition of the sweat has become the primary source of medical diagnosis as well. Because of this sweating defect many patients are unable to conserve salt, especially in hot weather, so that excessive sweating may lead to severe weakness and even death.

A second, and considerably more serious facet of the disease is based on the abnormality in the function of the mucus-secreting glands of the body. In cystic fibrosis, the mucus-producing glands fail to secrete their normal, clear, free-flowing fluid. Instead, they produce an abnormally thick, sticky mucus which tends to obstruct the ducts or openings of the glands. These abnormal secretions lead to a variety of serious complications. When the thick mucus accumulates in the ducts of the pancreas, it interferes with the function of this gland to supply digestive enzymes to the intestinal tract. Depending on the severity of this complication, the patient will suffer from malnutrition and its sequelae. The malnutrition of children with cystic fibrosis, combined with their repeated respiratory infections, results in general underdeveloped, poor musculature, and retarded bone growth.

The third most important complication involves the lung. Nearly all CF patients develop chronic lung disease at some time during their illness. Thick mucus deposits clog passages in the lungs or the branches of the windpipe, causing labored breathing or chronic cough. In time, bacteria may multiply in the accumulated secretions, and the child may fall victim to chronic bronchitis or even pneumonia. CF patients are extremely susceptible to lung infections and may succumb to pneumonia; lung disease accounts for 90 per cent of the deaths from this disease. Obstructed, damaged lung tissue may also impede blood circulation, and occasionally a child may die of chronic heart strain.

CF is the result of an inborn error of metabolism, inherited from parents who carry the genetic trait for the disorder. A carrier of the trait may not show any symptoms of the disease, yet is capable of passing the trait to his offspring, who, in turn, may transmit the disease. Cystic fibrosis is inherited in the active overt form when both parents carry the genetic trait. The genetic predisposition for cystic fibrosis may be passed on to the offspring of a couple if only one of the parents carries the trait. Thus for every overt case there is a large reservoir of occult carriers. As a matter of fact, this hidden affected population is reliably estimated at 2–5 per cent of the general population. Clearly, understanding and successful treatment of this disease would be a major public health achievement.

Although in the past cystic fibrosis was confined to the pediatric age group by its high mortality in infancy and early childhood, the disease is now recognized with increasing frequency among adolescents and adults. Recent studies have shown that there are far more adults than previously believed who carry a partial genetic endowment for the disease. The studies also have suggested that variants of cystic fibrosis may be responsible for some chronic

lung and gastroinestinal disorders in adults usually not recognized as due to cystic fibrosis.

Cystic fibrosis has the highest incidence and mortality rate of any of the hereditary diseases of children. As a killer of children under 15 years it outranks poliomyelitis, rheumatic fever and diabetes combined. Its increasing frequency throughout the world has made it a public health problem of no mean proportions; estimates of its incidence in the population range as high as 1 in 1000 live births. During the past six years, 25 state departments of health have included cystic fibrosis in their crippled children's program because of the very heavy expense for necessary and continuous care which families of afflicted children must meet.

RESEARCH DEVELOPMENTS AND TRENDS

The basic defect underlying cystic fibrosis is as yet unknown and much of the research carried on by scientists of the National Institute of Arthritis and Metabolic Diseases (NIAMD) in Bethesda and by Institute grantees is devoted to discovering its nature. Institute scientists in Bethesda are currently conducting laboratory and clinical studies in an attempt to delineate further the chemical and clinical manifestations of CF and to uncover the fundamental defect responsible for the disease. Trials are also being made to ascertain the best type of treatment for the chronic lung involvement which is the major cause of death. The relationship of this disorder to other types of chronic lung disease and gastrointestinal disorders is also being explored.

In addition to the research effort in Bethesda, the Institute supports financially approximately 30 different research studies of CF at non-governmental institutions throughout the country. During the past year a number of significant findings has been reported.

NEW DIAGNOSTIC TECHNIQUES

Early diagnosis and treatment of CF are of utmost importance in order to forestall in part development of irreparable lung damage and other serious complications of the disease. At the present time CF is diagnosed principally by the detection of excessive amounts of salt in the sweat. Sweat test facilities, however, are not always readily available, and results of such tests are not always conclusive.

Last year grantee scientists at Children's Hospital Medical Center in Boston devised a new, reliable diagnostic aid for CF whch involves analyzing samples of toenails, fingernails and hair for elevated concentrations of sodium and potassium. The new test also proved useful in identifying adults who are carriers of the CF trait; at present there exists no uniformly reliable method for positive identification of such individuals. Furthermore, nail and hair samples, because of their ease in collection and storage, may be forwarded by mail, thus providing ready access to specimens which may be of diagnostic or genetic interest.

Just a few months ago an engineer at Washington University, Seattle, working in close collaboration with the Boston grantees, reported that by combining nuclear reactor techniques with fingernail clippings from 170 kindergarten children he could markedly accelerate screening of such children for CF. The new test involves irradiation of nail clippings from the toes or fingers in a nuclear reactor for about an hour. The amount of sodium in the nail clippings is determined by measuring the amount of radioactive sodium produced during irradiation. Sodium levels in the nails indicate to the researchers whether or not the danger of cystic fibrosis exists. As many as 400 specimens each day can be analyzed by this technique, as opposed to about 20 daily by conventional chemical assay. Only 0.1 mg of nail is needed for the reactor test, while the chemical method requires 200 times that amount.

These investigators believe that the importance of early diagnosis in cystic fibrosis makes the test a valuable screening procedure for all admissions to a newborn nursery. Brothers and sisters of known cases may also be examined to determine whether they are hereditary carriers of the disease, a Mendelian recessive trait.

Another investigator at the University of Nebraska has devised a diagnostic test for CF which, although somewhat less conclusive than the sweat test, may be most useful when results of other diagnostic procedures are equivocal. The new test involves microscopic examination of a sample of rectal mucosa obtained painlessly from the patient. Abnormal rectal mucus glands characteristic of CF

are easily identified upon examination. Preliminary tests were performed on 24 infants and children with CF, and a positive diagnosis of CF was obtained in 16 subjects.

NEWBORN SCREENING TEST

Half the cystic fibrosis children who receive conventional, supportive therapy are dead by age three, while one third die in their first year. When prophylactic pulmonary therapy is added, however, mortality is reduced to about two per cent per year. A means of detecting cystic fibrosis in the newborn period promptly should further improve this outlook.

This past year an Institute-supported scientist reported a relatively simple, economical, and efficient sweat test for cystic fibrosis which can be applied routinely to newborn infants. Detection of cystic fibrosis in the newborn would permit earlier institution of prophylactic pulmonary therapy, thus increasing the life expectancy and decreasing the morbidity for cystic fibrosis children.

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 newborn nursery sweat test for cystic fibrosis.

PREDICTING CF

A new discovery has been made that will let couples know if their children are likely to inherit cystic fibrosis. For the first time a marker has been found in the blood of those diseased children and of parents who already have children with the disease.

It has long been known that cystic fibrosis is the result of a particular set of faulty genes in both parents. But until now no way was available of deciding accurately whether the fault was present in a potential parent or not. Now two pediatricians at Duke University, Durham, N.C., have found that when suitably concentrated blood fractions of parents of children with systic fibrosis—those *known* to carry the genes—are placed on tissues taken from the tracheae of rabbits, then the minute eyelash-like cilia which cover the exterior of these cells and, which normally beat with a uniform wave-like sweeping motion, beat erratically and irregularly. Irregularity of beating (or sweeping) occurs also when the blood samples from children with cystic fibrosis are used. The doctors do not know what chemical component in such blood indicates the presence or possibility of transmitting cystic fibrosis, but the results are reproducible, making the test useful.

Cilia are present in the air passages in the lungs of all animals, including man. They sweep the droplets of moisture and collections of mucus in the lungs to the foot of the trachea from where they are coughed out. Their failure to keep the lungs clear of mucus is one contributing factor to the lung congestion characteristic of CF.

PROMISING AGENT FOUND

In a study of relationships between the sympathetic nervous system, which innervates glands, and salivary secretions, a grantee of the National Institute of Dental Research has been able to alter the chemical composition of saliva from submaxillary glands in animals and humans. He reports that guanethidine has improved temporarily the chemical balance of the components of submaxillary gland saliva in 20 children with cystic fibrosis. The cloudiness of their saliva, as compared with the clear secretion of normal children, is apparently due to an unusually high proportion of organic substances as shown by large amounts of nitrogen, and of certain enzymes and other proteins.

On the basis of the experimental circumstances, the investigator concluded that guanethidine acts directly on the submaxillary gland tissue and not through mediation of the nervous system or hormonal controls. He points out that it is the first available agent to separate two factors—the organic (nitrogen, amylase, glycoproteins) and the calcium salt components—associated with abnormal submaxillary gland saliva in cystic fibrosis. This drug may be a useful tool to determine the primary defect in cystic fibrosis. Since the organic component of ex-

ternal secretions plays such an important role in the pathogenesis of cystic fibrosis and since its level in the submaxillary gland saliva can be normalized by guanethidine, this agent may well be a useful research tool for further therapeutic studies.

OUTLOOK

The genetic character of cystic fibrosis makes the disease particularly pernicious. As advances in therapy make it possible for young patients to reach the reproductive age, the "load" of cystic fibrosis traits in the genetic pool of the population will increase. If the basic genetic defect in cystic fibrosis and a method of correcting it permanently are not discovered, an ever-increasing sector of the population may find itself heir to the gene. It is this characteristic which makes continued support of effective research on cystic fibrosis an obligation to future generations.

Table of obligations

	1964	1965	1966	1967	1968
Cystic fibrosis and related areas:					
Research grants	$861,000	$899,000	$950,000	$1,052,000	$1,101,000
Intramural research	100,000	100,000	182,000	197,000	213,000
Collaborative studies			20,000		15,000
Total	961,000	999,000	1,152,000	1,249,000	1,329,000

Dr. WHEDON. We have been contributing actively to the support of research on this disease over the past several years. We have in our own direct operations research unit in Bethesda a laboratory of Pediatric Metabolism whose main purpose is devoted to learning more about this disease. They are concentrating at the moment on learning more about the physiology of the sweat glands, attempting to learn the basic defect in the disease which leads to the thickened secretions and the inability to clear infections from the lungs and impaired digestion, and so on.

PROGRESS ON CYSTIC FIBROSIS

Mr. CASEY. Are we getting anywhere? That is what I want to know. I know you have been doing some work on it, but are you making any progress?

Dr. WHEDON. Yes. We are finding that there are some very significant differences in the function of the sweat glands, that they behave in a different way from the normal sweat glands. Exactly where this will lead, I am not certain at the moment. I think the striking finding of the past year has been that there is some substance in the blood of patients with cystic fibrosis which, when applied to the lining of the respiratory tract in animals, stops the action of the cilia, which are the little hair-like projections which help so much in sweeping out the mucous and any dust or infectious material which may lodge in the breathing tubes, either of a human being or an animal. This rather striking finding lends further weight to our theory that it is a genetically transmitted disease, that not only patients but carriers of the disease have this peculiar chemical substance in their blood which interferes with ciliary action——

Mr. CASEY. You say not only patients but carriers?

Dr. WHEDON. Yes, sir.

Mr. CASEY. Is it a contagious disease?

Dr. WHEDON. No; it merely shows that they carry a partial chemical impairment and hereditary trait. The chemical processes in their cells

have a similar defect. But it is partial. It does not come out in full penetrance as they say genetically, so that they are able to function normally and do not have apparent disease, or if they have it, it is in a very, very mild form.

Mr. CASEY. That is what you called a carrier?

Dr. WHEDON. That is right.

Mr. CASEY. Is it transmitted to their children?

Dr. WHEDON. They can transmit it to their children.

Mr. CASEY. Is it only transmitted through the mother or is it transmitted through either parent, or do you know enough about that yet?

Dr. WHEDON. I do not believe we have worked out fully the genetics of this disease.

Mr. CASEY. How long have you been working on it?

Dr. WHEDON. I would say actively on this program about 8 years.

BUDGET FOR CYSTIC FIBROSIS

Mr. CASEY. How much are you spending on it?

Dr. WHEDON. The present level in this fiscal year is $1,250,000.

Mr. CASEY. What did you spend last year?

Dr. WHEDON. The year before, $1,150,000.

Mr. CASEY. You are not asking for much of an increase, then?

Dr. WHEDON. I am sorry, sir?

Mr. CASEY. Just a hundred-thousand-dollar increase?

Dr. WHEDON. Yes, between 1966 and 1967.

Mr. CASEY. Do you have any census on how many cases of cystic fibrosis you have?

Dr. WHEDON. It occurs about once in every 2,000 live births. We believe it is the second most common post-mortem diagnosis in children's hospital. We feel that the number of genetic carriers may be anywhere from 2 to 20 percent of the full population. I do not have before me the actual estimate of the total number of cases, but I think we could calculate that.

DEATHS RESULTING FROM CYSTIC FIBROSIS

Mr. CASEY. Approximately how many children do you think die of cystic fibrosis each year?

Dr. WHEDON. I would estimate very roughly that it was in the neighborhood of 20,000. I would like to check that figure, Mr. Casey.

Mr. CASEY. What were we talking about the other day, about 50,000 die of lung cancer. What are we spending on research on lung cancer? You probably do not know. It is a great deal more than $1,250,000; is it not?

Dr. WHEDON. I can only add that this is an extraordinarily difficult problem. It is one that we recognized as difficult back about 6 to 7 years ago so that we tried to enlist the interest of the biomedical research community by holding a conference here in Washington. We have since held another conference about 2 years ago. We have had real difficulty in getting scientists who are particularly trained in protein chemistry and other related important disciplines to really attack this disease.

I might add, Mr. Casey, that I am prompted here that there are about a total of 5,000 to 10,000 cases of cystic fibrosis in the United States. So that my first figure of 20,000 deaths would be far to high. Based on a birth rate of 20 per thousand, 200 million total population and one case of cystic fibrosis per 2,000 live births, if all cases died, the maximum figure would be 2,000.

Mr. CASEY. I do not know whether it is or not because many of them do not live very long after birth. You have all stages of it. Some only live a few days after birth, some just a few months, some just a few years, and those with a less serious case may last until they are 7 or 8 years old.

Dr. WHEDON. The situation has improved considerably over that just in recent years because of improved care, particularly of the infections in the lung and better nutrition management. So there now have been quite a number of patients who have lived into their teens and twenties and some have married. In fact, there are a total now of about 10 children born of mothers with definite cases of cystic fibrosis.

Mr. CASEY. That is nothing we can really brag about, though, is it, in attacking this disease?

Dr. WHEDON. I agree with you wholeheartedly. It is a very serious problem.

DIFFICULTY OF MOUNTING VIGOROUS CYSTIC FIBROSIS PROGRAM

Mr. CASEY. You say you could not get enough interest. What does it take to generate interest to attack this? Do you have to get a lot of people to attend a conference to generate a lot of interest? I did not quite get what you stated. You said you had trouble generating interest and had held one meeting and there was very little interest or attendance. Is that what you said?

Dr. WHEDON. The people who attended were certainly interested, but they found sufficient difficulty in trying understand how to attack this problem that progress has indeed been very slow.

Dr. SHANNON. I would like to comment on that. Mr. Casey, I think this is a very good example of a disease of obvious importance. I think the last 6 or 7 years shows that it affects many tissues, particularly the gastrointestinal tract, respiratory tract, and the skin. It is accompanied by a great susceptibility to infection. There is no simple treatment available. Indeed, there is available no simple entry into the problem. What this program constitutes at the present time is a probing to find ways to enter the problem. Until that break comes, no amount of money available to the general public will bring productive work because the leads are so slim as to defy the development. If you gave us a large sum of money and said, let us develop a developmental program and solve this problem, the information we have on this at this particular stage would preclude the mounting of a vigorous developmental program in the area.

I think until some break appears—this blood factor may well be that—I would point out that one of the problems of biomedical science is that we are still in many areas in the exploratory stages of the study of disease. We still are shockingly naive about what common procedures will do.

Last evening I was reading a report in the Medical World News that I am sure was sparked in part by the difficulties that NASA got in the high oxygen tensions. This called a lot of people's attention to the oxygen; not the flame, but the carrying of astronauts in high oxygen tensions for long periods of time. It turns out that such a realtively simple thing as the exposure to high oxygen tension at atmospheric pressure with about 30 to 40 percent oxygen, for a limited number of days, is invariably accompanied by discernible profound damage to the lung. We have been using oxygen therapeutically ever since pulmonary disease was established; yet for some extraordinary reason this observation was made in three different clinics within the same year with complete confirmation clinic to clinic, and indicates that the giving of oxygen for the simple relief of respiratory distress is not in itself without any hazard. I read that last evening and thought back on my own experience as to how we have used oxygen in a variety of things for so many years as what we thought to be a lifesaving measure, but not infrequently the very tool we used as a lifesaving measure, and it might well have been lifesaving, in itself carried another hazard. I think that we as medical scientists would be the last to boast of our knowledge. We are more prone to be very humble about our great ignorance about some of these things.

When you take a complex disease like cystic fibrosis, which particularly affects the very young, that are peculiarly hard to work with in an experimental situation, where the overriding presenting symptom is usually one of infection which is a secondary phenomenon rather than a primary phenomenon, it is just very difficult to really mount a program of honest exploration. Where we make progress in the medical sciences is usually where we can develop animal models that give us an ability to do things that you cannot possibly do in human experimentation. Where you can precipitate certain crises and see the extent to which these can be removed. When you have a disease, however serious it may be, at the present stage of our knowledge, such as cystic fibrosis, or membrane disease of the infant, which equally causes a large number of deaths, we do not have the ability with our present knowledge to define specifically the factors in such a way as to permit a really intensive program. We must undertake these studies in a probing nature, realizing that many things we do will be fruitless, but nonetheless go down the line with every possible approach to it until a break appears. When the break appears then movement takes place. But in this particular disease this break has not come. It is discouraging, sir, but these are the facts.

Mr. CASEY. Let me ask you this: You do not carry it on a low priority by any means, I trust?

Dr. SHANNON. No, sir.

Mr. CASEY. I presume you are encouraging research in the field?

Dr. SHANNON. This indeed we are. The importance of a disease of this nature, as Dr. Whedon said, led us to set up a fairly comprehensive group within our laboratory because we did not think we would be able to engage others in the particular type of work that we were convinced is so important. I think it is unfortunate that there is not a broader research effort, but in the absence of clear-cut leads, the probing type of inquiry that may eventually uncover a

means for coping with the disease must be the order of the day. This is not because we think it unimportant.

Mr. CASEY. I sincerely hope you keep that in mind because I think it is a very challenging field.

Dr. SHANNON. Yes, sir.

Mr. CASEY. As you say, it is something that evidently very little is known about, and it does take a tremendous toll of youngsters. I sincerely hope you do find a breakthrough where you can move forward in the very near future.

Dr. WHEDON. I assure you that we have cystic fibrosis very much in mind.

Mr. CASEY. That is all, Mr. Chairman.

RESEARCH ON SAFE DOSAGE LEVEL OF ASPIRIN

Mr. SMITH. The Institute supported research to determine the safe dosage level for aspirin, did it not?

Dr. WHEDON. The studies with which I am familiar have been studies in which comparisons were made between the effectiveness of aspirin and other compounds in the treatment of rheumatoid arthritis.

Mr. SMITH. I am referring to your report on page 6. It says the grantees found that pouch bleeding did not occur at the initial salicylate dose level but was significant at a larger dose level, it increased and it gives the ccs. I notice FDA now is undertaking a study to determine the safe dosage level for aspirin. Is there a duplication or what is the difference in the studies and was the result of your study made available to them.

Dr. WHEDON. Could you tell me, sir, in which report you are looking?

Mr. SMITH. On page 6.

Dr. WHEDON. My only comment is that I doubt very seriously that there is any overlap and duplication. This was a study in a special preparation in dogs in which there were special stomach pouches. I imagine that the FDA approach will emphasize a considerable interest in the effects in human beings. Nevertheless, we shall make certain that they are aware of this particular study which we supported.

Mr. SMITH. Would you further expand on your answer in the record?

(The information to be supplied follows:)

The study referred to on pages 5 and 6 of the December 1966 Special Report on Gastroenterology can be summarized as follows:

In the past, there have been numerous observations, clinical and experimental, demonstrating a causal relationship between gastrointestinal bleeding and ingestion of salicylate compounds, including aspirin (acetylsalicylic acid). Previous research has shown an erosive mucosal irritation after aspirin ingestion. This has led to the belief that salicylates cause gastrointestinal hemorrhaging by direct mucosal irritation.

In recent experiments, Institute grantees at Marquette University have succeeded in inducing bleeding in isolated, denervated stomach pouches (*Heidenhain* pouches) of dogs after oral administration of salicylates. Similar observations have been made previously by others using innervated *Cope* pouches, but the observed bleeding was not quantitated, and in such pouches the action of nervous stimuli conveyed via the still intact nerve supply, cannot be ruled out.

The grantees found that pouch bleeding did not occur at the initial salicylate dose level, but was significant at a larger dose level. During the third *control* period the mean daily blood loss from gastric pouches was 0.292 cc, compared to a mean of 3.12 cc during the third *treatment* period. Choline salicylate had no significant effect on pouch bleeding. Thus, because bleeding occurred in the denervated, isolated pouches (which were never in direct contact with the drug) as a result of acetylsalicylic acid delivered to the main portion of the stomach, the Institute grantee's findings suggest that a *blood-borne* mechanism, as yet unidentified, may be responsible for gastric bleeding in some cases.

In answer to Congressman Smith's question, it should be emphasized that this experiment in denervated stomach pouches in dogs is attempting to investigate the precise *mechanism* through which aspirin and other salicylates induce bleeding in the stomach lining of the recipient. This experiment suggests that aspirin-induced gastric bleeding may not only be due to the direct irritating effects of the drug on the stomach lining, but that in addition, another mechanism may be involved, namely a blood-borne messenger mechanism as yet unidentified (this mechanism may act through a blood-borne chemical substance). This type of experiment has little in common with the type of studies through which, as we understand it, the Food and Drug Administration is attempting to determine the safe dosage level for aspirin *in man*. In the latter type of experiment the emphasis is on the safety and on any possible deleterious effects of the repeated and long-term administration of salicylates in man—such as may be found in individuals who are taking large quantities of aspirin and related salicylates to combat the pain of arthritis, muscular aches and pains, or headaches, and whose daily long-term aspirin intake may thus become a problem if aspirin toxicity at such levels is proved. Nevertheless, we shall be delighted to forward a summary of the specific aspirin study at Marquette to the proper individuals in the Food and Drug Administration.

Mr. SMITH. That is all, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Whedon.

JUSTIFICATION MATERIAL

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Amounts available for obligation

	1967	1968
Appropriation	$135,687,000	$143,954,000
Comparative transfers within NIH	−980,000	
Transfer to "Operating expenses, Public Buildings Service," General Services Administration	−12,000	
Total	134,695,000	143,954,000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grant:						
Research		$90, 629, 000		$96, 304, 000		+$5, 675, 000
General research support grants		(8, 286, 000)		(9, 842, 000)		(+1, 556, 000)
Scientific evaluation and planning		(20, 000)		(20, 000)		(0)
Categorical clinical research centers		(1, 500, 000)		(1, 500, 000)		(0)
Fellowships		6, 129, 000		6, 591, 000		+462, 000
Training		14, 857, 000		15, 706, 000		+849, 000
Direct operations:						
Laboratory and clinical research	531	13, 248, 000	541	14, 333, 000	+10	+1, 085, 000
Collaborative research and development	25	5, 124, 000	26	7, 736, 000	+1	+2, 612, 000
Biometry, epidemiology and field studies	26	730, 000	28	751, 000	+2	+21, 000
Review and approval of grants	79	1, 924, 000	81	2, 157, 000	+2	+233, 000
Program direction	22	$330, 000	25	$376, 000	+3	+$46, 000
Total obligations	683	132, 971, 000	701	143, 954, 000	+18	+10, 983, 000
Unobligated balance, reserve		1, 724, 000				−1, 724, 000
Total, obligations and balance	683	134, 695, 000	701	143, 954, 000	+18	+9, 259, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	683	701	+18
Full-time equivalent of other positions	18	18	0
Average number of all employees	670	711	+41
11 Personnel compensation:			
Permanent positions	$6, 437, 000	$6, 701, 000	+$264, 000
Positions other than permanent	190, 000	190, 000	0
Other personnel compensation	50, 000	50, 000	0
Total personnel compensation	6, 677, 000	6, 941, 000	+264, 000
12 Personnel benefits	688, 000	708, 000	+20, 000
21 Travel and transportation of persons	265, 000	330, 000	+65, 000
22 Transportation of things	60, 000	60, 000	0
23 Rent, communications and utilities	158, 000	175, 000	+17, 000
24 Printing and reproduction	55, 000	60, 000	+5, 000
25 Other services	886, 000	1, 114, 000	+228, 000
Project contracts	5, 020, 000	7, 650, 000	+2, 630, 000
Payment to "National Institutes of Health management fund"	5, 766, 000	6, 448, 000	+682, 000
26 Supplies and materials	1, 105, 000	1, 115, 000	+10, 000
31 Equipment	694, 000	770, 000	+76, 000
41 Grants, subsidies, and contributions	111, 615, 000	118, 601, 000	+6, 986, 000
Subtotal	132, 989, 000	143, 972, 000	+10, 983, 000
Deduct quarters and subsistence charges	18, 000	18, 000	0
Total obligations by object	132, 971, 000	143, 954, 000	+10, 983, 000

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SUMMARY OF CHANGES

1967 enacted appropriation	$135,687,000
Unobligated balance reserve	−1,724,000
Comparative transfers within NIH	−980,000
Transfer to "Operating expenses, Public Buildings Service," General Services Administration	−12,000
Total estimated obligations, 1967	132,971,000
1968 estimated obligations	143,954,000
Total change	+10,983,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in:				
1. Annualization of new positions authorized in 1967				$45,000
B. Program:				
1. Research grants		$90,629,000		5,675,000
2. Fellowships		6,129,000		462,000
3. Training grants		14,857,000		849,000
4. Laboratory and clinical research	531	8,834,000	10	597,000
5. Collaborative research and development	25	5,090,000	1	2,604,000
6. Biometry, epidemiology, and field studies	26	695,000	2	9,000
7. Review and approval of grants	79	750,000	2	52,000
8. Program direction	22	221,000	3	28,000
Subtotal, program increases			18	10,276,000
C. Centrally furnished services from the National Institutes of Health management fund:				
1. Laboratory and clinical research		4,414,000		479,000
2. Collaborative research and development		34,000		4,000
3. Biometry, epidemiology, and field studies		35,000		6,000
4. Review and approval of grants		1,174,000		179,000
5. Program direction		109,000		14,000
Subtotal, management fund		5,766,000		682,000
Total, increases				11,003,000
DECREASES				
One less day of pay in 1968				−20,000
Total net change requested			+18	+10,983,000

EXPLANATION OF CHANGES

Research grants—The program increase of $5,675,000 will provide $1,556,000 for general research support grants and $4,119,000 for an estimated additional 46 research projects and general increased average costs.

Fellowships—The increase of $462,000 will provide for an estimated additional 24 fellowships in 1968.

Training grants—The increase of $849,000 will provide for an estimated additional 8 new training centers and for increased average costs in the existing centers.

Laboratory and clinical research—The increase of 10 positions and $597,000 will provide for strengthening of clinical investigations, chemical biology and physics, and scientific reporting; for the purchase of additional electronic computing services; and for renovation and equipping of additional space to be provided by relocation of the NIH library.

Collaborative research and development—The increase of one position and $2,604,000 will provide for continued development of the Artificial Kidney-Chronic Uremia Program, and modest strengthening of the scientific communications program.

Biometry, epidemiology and field studies—The increase of 2 positions and $9,000 will provide required assistance for present and planned epidemiological and clinical field studies in the Southwestern United States.

Review and approval of grants—The increase of 2 positions and $52,000 will provide for strengthening of grants management and analysis activities, and for required electronic data processing costs.

Program direction—The increase of 3 positions and $28,000 will provide a modest strengthening of Institute management staff and for required program analysis assistance with reference to Institute programming and budgeting systems.

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.

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 disease. . . ."

"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."

Explanation of transfers

	1967 estimate	1968 estimate	Purpose
Transfer to "Operating expenses, Public Buildings Service", General Services Administration.	$12,000	----------	For rental of Westwood office building.
Comparative transfer to—			
Other NIH accounts	380,000	----------	Redistribution of the National Institutes of Health management fund.
"General research and services," National Institutes of Health.	600,000	$600,000	United States-Japan cooperative medical science program.

RESEARCH GRANTS

	1967 estimate	1968 estimate	Increase (+) or decrease (−)
Research projects	$80,823,000	$84,942,000	+$4,119,000
Special programs	9,806,000	11,362,000	+1,556,000
Total research grants	90,629,000	96,304,000	+5,675,000

INTRODUCTION

Since its establishment in 1950 as an Institute, the National Institute of Arthritis and Metabolic Diseases role in the Federally-supported campaign against disease has been one of growing responsibility. Originally charged with the conduct and support of research into the causation, diagnosis, and treatment of the various arthritides, the rheumatic and collagen diseases, and metabolic disorders, such as diabetes, this initial responsibility has been broadened to encompass many other disease categories. Among them are endocrine disorders, diseases of the gastrointestinal tract, including diseases of the liver and gallbladder, diseases of the blood and bone, urological disorders and diseases of the kidney, numerous other metabolic disorders, both acquired and inherited, such as cystic fibrosis, and the fields of nutrition, orthopedic surgery and dermatology.

In pursuit of these goals, relevant fundamental research encompasses the disciplines of biochemistry, chemistry, biology, molecular biology, anatomy, physiology, enzymology, pharmacology, pathology, histology, toxicology and genetics, as they relate to life processes in health and to diseases that fall within Institute purview. Emphasis is placed on the conduct and support of research in fundamental sciences which constitute the foundation of knowledge pertinent to these diseases. There is an urgent and continuing need to expand these research activities not only from the point of alleviating the suffering of millions afflicted with disease but also to further the concept of preventive medicine. As more basic knowledge is obtained through research about normal life processes and factors that create disease or disease conditions, more effective medical means can be found to prevent or minimize diseases or their effect on the body. This is the ultimate goal, one which demands a much greater body of knowledge than is presently available.

PROGRAM PLANS IN 1967 AND 1968

Arthritis and Rheumatic Diseases

Although lacking the dramatic impact of the "killer" diseases, arthritis is by far the Nation's leading crippler. Because arthritis tends to cripple and disable rather than to kill, it ranks high on the list of chronic diseases from the standpoint of social and economic impact. It causes its victims more prolonged mental anguish and physical pain, agony and misery than any other group of diseases. Surgeon General William H. Stewart recently termed arthritis a national *medical* as well as *economic* problem. This evaluation is more than borne out by Public Health Service health statistics which estimate that approximately 13 million Americans today are afflicted with some form of arthritis or related disorder. The economic impact of this insidious disease, no less astounding than the number of victims, is now estimated to be approaching an annual cost of almost $4 billion to the Nation, including losses in tax revenue, costs of disability and other payments, costs of hospitalization, physicians' visits, drugs, physical therapy, nursing home care, and other services.

Of the estimated 13 million Americans suffering from arthritis, about 700,000 are so incapacitated as to be unable to work, maintain a home, attend school, or or engage in any recreational activities. The remainder suffer from varying degrees of limitations and restrictions. As a cause of restricted activity and bed disability, arthritis is exceeded only by heart disease, as a workloss cause, it is exceeded by heart disease and gastrointestinal ulcers only. Disability from arthritis in the United States causes an estimated 186 million days of restricted activity, including 57 million bed-ridden days and 12 million days lost from work, each year.

The primary goal of research in the field of arthritis is to discover the cause or causes of rheumatoid arthritis, osteoarthritis, and related disorders. Equally important goals of this program are to improve existing forms of treatment and management, and to determine means of preventing arthritis.

Additional funds provided by the Congress in 1967 for increased efforts in this field are being employed for the establishment of an Arthritis Coordinated Clinical Investigation Program. This will involve a group of clinical investigation centers of excellence working in close coordination in pursuit of possible solutions and improved therapy utilizing most recent findings, techniques, and developments of promise. Particular attention is being devoted to indomethacin and other new therapeutic agents.

The main thrust of present and future research will be into an area where promising new etiologic possibilities recently have been uncovered. Two types of microorganisms recently found to be implicated in joint diseases will be studied in relation to rheumatoid arthritis. Intensive investigations are planned on the possible role of mycoplasmas (microorganisms with characteristics of both bacteria and viruses) in causing rheumatoid arthritis, and viruses belonging to the genus *Bedsonia*. Arthritis has been produced in monkeys by injecting them with Bedsonia organisms isolated from human patients with Reiter's syndrome, a disease closely related to rheumatoid arthritis.

Diabetes

Of all the inherited metabolic diseases for which research responsibility lies, diabetes mellitus is the more important and widespread. Today, 4 million Americans are known diabetics. An estimated 5 million more are potential victims. Diabetes ranks 7th as a cause of death due to disease, but this is a

misleading, low mark since the disorder contributes significantly to cardiac and cerebrovascular deaths through its vascular complications. The most obvious defect in diabetes is the body's inability to metabolize carbohydrates normally. Underlying the disorder is a basic impairment of insulin activity. Although diabetes today can be controlled fairly well with injections of insulin, through the use of oral antidiabetic drugs, and by the use of dietary measures and controls, there remains considerable need for further improvements in the treatment of this disease and for more effective measures to prevent or to ameliorate its serious complications which are responsible for much of the disability and morbidity connected with the disorder.

Immediate research activities and objectives of this Institute in diabetes focus on: elucidation of the nature of the interference with normal insulin activity and of substances which destroy or inactivate insulin after its release from the pancreas; possible modification of recently synthesized insulin fractions or of fractions of insulin from other species to provide a therapeutically effective hormone for improved management of diabetes and to serve as a research tool in studying the mechanism of action of insulin; specific studies designed to suppress development of vascular and neurological complications; studies to improve control of "brittle" or juvenile diabetes; and studies to explore possible use of the oral antidiabetic drugs in postponing the onset of overt diabetes in asymptomatic individuals genetically destined to develop this disorder.

Other Inherited Diseases of Metabolism

While diabetes is the most important and most widespread of the inherited metabolic diseases, other serious hereditary metabolic disorders for which this Institute bears responsibility include: gout, cystic fibrosis, certain blood disorders, phenylketonuria, galactosemia, Wilson's disease, alcaptonuria, histidinemia, homocystinuria, and various glycogen storage diseases, familial Mediterranean fever, congenital non-hemolytic jaundice and many others.

Research plans in these areas will focus on the development of new and more reliable patient management by use of specific drugs, such as copper chelating agents in Wilson's disease, or through specialized diets, as in the galactose-free diet in galactosemia.

Metabolic and Endocrine Disorders (unrlcated to genetics)

Studies belonging to this category comprise fundamental research on normal metabolic processes, studies on non-hereditary metabolic disorders, and investigations in the field of endocrinology and of endocrine disorders. All living cells have in common the phenomenon of "metabolism," consisting of an infinite variety of chemical reactions through which the cells derive energy for life processes and produce various chemical substances needed for life, growth and reproduction. Hormones, the specialized chemical messenger substances produced in the endocrine glands of the body are capable in some instances of modifying specific metabolic reactions and in other of modulating an individual's sexual differentiation before birth, his growth, intellectual development, vigor and drive, reproduction, and senescence. Therefore, through their effects on human metabolism, physiology, and morphology, hormones regulate practically all human normal activity and exert profound influence on a wide array of disorders within the Institute's area of responsibility.

Current understanding of hyperthyroidism and hypothyroidism and the known effective methods of therapy and long-term management came about through detailed knowledge of thyroid hormones and of the pituitary hormone thyrotropin which affects the endocrine output of thyroid gland. Similarly, corticosteroid therapy, which is invaluable in treating rheumatoid arthritis, Addison's disease, asthma and other serious conditions, is the outgrowth of our basic understanding of the steroid hormones of the adrenal gland.

In addition, fundamental research which led to the isolation and purification of the pituitary human growth hormone (HGH) now allows some children afflicted by hypopituitary dwarfism to attain a substantial measure of growth through HGH replacement therapy. Due to the scarcity of HGH (its only sources are pituitary glands obtained at post-mortem examination), its synthesis holds out the greatest hope for therapy on a large scale for dwarfism. Toward this end, Institute-supported investigators are endeavoring to arrive at an effective method of laboratory synthesis of HGH or to derive a human growth stimulating function from *bovine* growth hormone, by modifications of this substance.

Research progress in this field, however, is hindered by the lack of fundamental knowledge of the precise mechanisms by which hormones influence metabolism and how they cross-react with each other. A particular obstacle is incomplete knowledge of the exact nature of the structure of cellular membranes which determine the transport of metabolites in and out of cells. The molecular structure of most hormones is not as yet known and there is a lack of pure and potent preparations of endocrine hormones to aid research. Sensitive assays for specific human studies are just being developed. Furthermore, this field of research is hampered by an insufficient number of highly trained, sophisticated investigators.

Of particular significance in research in the last year was the elucidation by a grantee of the composition and structure of human growth hormone, thereby enhancing chances for its eventual synthesis in the laboratory, a prime goal of the Institute.

Gastroenterology and Liver Disease

Ailments of the gastrointestinal tract are among the most common serious illnesses that afflict modern man. This illness ranks second only to heart and circulatory diseases in the number of required physicians' office visits or house calls. Gastrointestinal ailments include peptic ulcer, regional enteritis, ulcerative colitis, cirrhosis of the liver, gallbladder diseases, pancreatitis, diverticulitis, intestinal malabsorption, and many others. Often, these diseases result in prolonged and expensive hospitalization and innumerable social and economic problems.

The extent of their social and economic impact may be clearly visualized in figures published in 1966 by the Public Health Service in a study entitled "Estimating the Cost of Illness." According to this study, direct expenditures for diseases of the digestive system in 1963 were estimated at $4.2 billion, higher than direct costs for any other disease category. Another $1.3 billion in indirect costs also were attributed to diseases of the digestive system. The cost in terms of lost man hours and direct medical expenses due to peptic ulcer alone is estimated at $500 million annually. About 14 million Americans, or over 7 percent of the entire U.S. population, now have or have had an ulcer of the duodenum or stomach. According to health statistics, an estimated 4,000 individuals develop an ulcer each day, and about 10,000 die of complications of peptic ulcer every year.

Despite significant gains in knowledge, much yet remains to be learned and understood about these disorders. The causes of many gastrointestinal diseases are still unknown, or not fully comprehended, and new methods and techniques of investigation, diagnosis and therapy have been limited. In broad terms, gastrointestinal disorders may be outlined as follows: to increase the basic scientific and clinical understanding of the fundamental processes of digestion, absorption, secretion, excretion and other functions of the gastrointestinal tract, liver and gallbladder in order to improve their medical and surgical treatment; to elucidate more completely the neuronal and hormonal control of digestive secretion; to devise new medical and surgical treatments in gastrointestinal disease, and in the case of acute liver disease, a growing concern in this area, to provide novel treatment systems to sustain patients through acute liver failure while allowing regeneration of their own functioning liver tissues.

More specifically, Institute-supported research now and in the immediate future will endeavor to extend biochemical studies of enzyme and hormone action in intestinal absorption; emphasize studies of the disordered metabolism of liver failure; develop new surgical methods of treatment of gastrointestinal diseases and new medical treatment modalities, including drugs; develop new research tools and techniques to permit examination of previously inaccessible or difficult areas of the gastrointestinal tract; study of variety of metabolic processes taking place in the cells lining the stomach, intestines and gallbladder so as to relate these processes to gross physiologic activity in normal and abnormal conditions; use the newly synthesized hormone, gastrin, for assessment of gastric secretory function. In connection with the latter, in 1966 we reported on the synthesis of gastrin by Institute-supported investigators. This hormone which originates in the mucosa of the lower end of the stomach stimulates secretion of gastric juices. Gastrin synthesis is important especially for research in peptic ulcer, a disease condition about which little new knowledge has been gained in recent years. It has been known that peptic ulcer victims, particularly those with the duodenal variety, secrete an excess of acid digestive juices but the mechanisms controlling secretion under normal and abnormal conditions have remained obscure. The synthesis of gastrin not only provides a potent secretory

stimulant for assessing gastric function but also is important because it opens up entirely new approaches for research in the area of peptic ulcer.

Kidney and Urologic Diseases

Disorders of the kidney cover a wide range of diseases entities and stem from an equally wide variety of conditions, including hypersensitivity infections, circulation, metabolic, developmental disorders, and obstruction conditions. Among the more common diseases of the kidney are: glomerulonephritis, pyelonephritis, the enphrotic syndrome, and the hypertensive kidney disease. With the passage of time these diseases, regardless of their original cause, tend to progress to a common-end stage with a common clinical picture, uremia, with eventual fatal results. Kidney diseases are particularly important as causes of death in individuals in their middle, most productive years, with 50 percent of such deaths occurring in patients under 65 as compared with 28 percent for heart disease and 19 percent for stroke. Most recent figures compiled by the PHS National Center for Health Statistics indicate that almost 25,000 Americans died of kidney disease in 1964. It is believed that the actual number of annual deaths caused by kidney disease, directly or indirectly, is considerable larger since the latter figure does not include deaths attributed to conditions such as hypertension or stroke which may be secondary to an underlying kidney ailment.

Overall, the goals of the Institute's research activities in this field are to increase the understanding of and to improve the therapy and means of preventing kidney diseases; to obtain a better understanding of the uremia syndrome; and to provide more efficient, economical management of patients with advanced renal failure through development of inexpensive, simple and more effective chronic dialysis treatment. A more distant but ultimate goal is development of long term replacement therapy by kidney transplant. A prime drawback to more rapid progress in the hemodialysis is lack of knowledge concerning specific toxic substances or metabolic products which accumulate in the bloodstream during renal failure and which are responsible for the toxic symptomatology in uremia. Other important general obstacles involve lack of fundamental knowledge of normal kidney biochemistry and physiology and of the pathogenesis and etiology of various forms of renal and urological disease.

In 1966, Institute-supported investigators made significant contributions toward identifying and characterizing the toxic factors in uremia. A study of patients with nephrotic syndrome revealed that such patients have a general cancer incidence 10 times that of comparable population groups. In other research areas, grantees have markedly reduced early failure of kidney homografts by a program of "renal-protective" management (hydrating the living kidney donors immediately before the operation); clarified an aspect of the immune response in kidney homotransplantation; prolonged survival of canine kidney transplants by treating recipient dogs with horse antiserum to dog lymphocytes; and obtained evidence that there is essentially no correlation between the presence of positive urine cultures, positive renal tissue cultures, and the histologic diagnosis of chronic pyelonephritis in juvenile diabetic patients—suggesting that factors other than the continued presence of bacteria in the kidney play a role in the pathogenesis of chronic pyelonephritis.

Anemias and Other Blood Disorders

The number of individuals afflicted with anemias and other blood disorders in this country is considerable. Many of these conditions are truly hereditary or are conditioned by genetic factors. Among the more prominent blood disorders needing solution are: sickle cell anemia and other genetically transmitted abnormalities of the hemoglobin molecule; chronic hemolytic anemias, such as thalassemia or Mediterranean anemia; clotting disorders such a hemophilia, Rh incompatibility, and neonatal thrombocytopenic purpura, a platelet deficiency and bleeding problem in newborn infants. Examples of relatively frequently found abnormalities or disorders in this grouping are sickle cell anemia and Rh incompatibility. Sickle cell aneima affects a significant percentage of Negroes and is associated with considerable disability and shortened life span. Rh incompatibility is an obstetrical complication affecting a recognizable percentage of the population due to the mixed blood type of individual parents.

The field of platelet and white blood cell typing is closely related to the general field of tissue typing, and has, thus, a profound effect on the entire field of organ transplantation; knowledge in this area is now just beginning to unfold. The aims of Institute research support in the field of anemias and blood dis-

orders are to gain a better understanding of blood diseases, their basic causes, treatment and prevention, and to clarify the role of blood factors and elements in coagulation and in certain immunity reactions. In support of these goals, research planning in the present and immediate future encompasses: development of improved methods of treatment, long term management, or prophylaxis of the various major blood disorders; development of practical antihemophilic factor preparations for treating bleeding in hemophilic patients and for prophylaxis before elective surgery; programmed studies on the genetic transmission of the hemophilia trait, sickle cell anemia, and other hereditary blood disorders, with a view toward meaningful genetic counseling; programmed studies on the Rh antigen of red blood cells and of improved prophylactic and therapeutic means of coping with Rh incompatibility in obstetrics; a programmed investigation of blood clotting mechanisms, with emphasis on clarifying the physiological and biochemical action of small peptides released during blood clotting; and increased emphasis on clarifying the immunologic aspects of coagulation disorders and of the structure of fibrinogen, thrombin and hemoglobin. Additionally, emphasis will be placed on understanding the mechanisms of thrombocytopenic purpura and of the composition, structure and characteristics of serum proteins as a mechanism in understanding macroglobulinemia and disproteinemia.

Dermatology

With the execption of pemphigus and long-standing skin cancer, most disorders of the skin are not life threatening. They represent, however, very widespread conditions which can be extremely disabling and incapacitating, both physically and psychologically.

The current state of knowledge in psoriasis graphically illustrates the problems now faced in dermatologic research. Psoriasis is a relatively common, noncontagious skin disorder in which faulty epidermal (skin) metabolism results in disfiguring lesions on the skin surface. The basic cause of psoriasis is unknown, and the disorder occurs in from three to five percent of the population, of which from one to two percent constitute severe cases. Current knowledge of psoriasis and other skin diseases, such as atopic dermatitis, pemphigus, and discoid lupus erythematosus, is inadequate with respect to therapy and basic knowledge of skin physiology. Although skin has certain advantages as a research tool because of its ready availability, it has failed to attract adequate numbers of high quality independent investigators. Because of inadequate knowledge of fundamental concepts, practice and therapy in the field of dermatology, it has remained largely nonspecific, symptom-relieving and empirical, although much aided in recent years by the availability of specific drugs (antihistamines and steroids).

Because basic research in dermatology is still a relatively young and new area of clinical science, the Institute's program in dermatology may be characterized as a probing inquiry into an extremely important field, at a relatively low cost. The program envisioned by the Institute will aggressively seek to expand the fundamental knowledge of both normal and abnormal skin with regard to composition, metabolism, and responses to outside stimuli; to gain better understanding of specific pathogenesis in the various skin disorders; and to devise effective therapy and prophylactic measures. Further, it is planned to attract into laboratory and clinical research in dermatology additional well-qualified, research-motivated investigators who have the skills to attain the goals set by the Institute.

Research grants program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
1. Arthritis	$6,493,000	$6,635,000	+$142,000
2. Dermatology	1,782,000	1,871,000	+89,000
3. Diabetes	4,377,000	4,596,000	+219,000
4. Endocrinology	12,840,000	13,583,000	+743,000
5. Gastroenterology	10,526,000	11 386 000	+860 000
6. Hematology	6,067,000	6,927,000	+320,000
7. Metabolism	20,272,000	21,216,000	+944,000
8. Nutrition	6,432,000	6,754,000	+322,000
9. Orthopedics	3,401,000	3,571,000	+170,000
10. Urology and kidney diseases	5,193,000	5,453,000	+260,000
11. Other or interrelated areas	2,900,000	2,950,000	+50,000
12. Subtotal	80,823,000	84,942,000	+4,119,000
13. General research support grants	8,286,000	9,842,000	+1,556,000
14. Scientific evaluation and planning	20,000	20,000	
15. Categorical clinical research centers	1,500,000	1,500,000	
16. Total obligations	90,629,000	96,304,000	+5,675,000

Distribution of research grants

[Dollars in thousands]

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	1,644	$52,103	1,682	$54,445	+38	+$2,342
2. Competing projects	781	26,300	789	27,732	+8	+1,432
3. Supplementals		2,420		2,765		+345
4. Subtotal regular program	2,425	80,823	2,471	84,942	+46	+4,119
5. General research support grants		8,286		9,842		+1,556
6. Scientific evaluation		20		20		0
7. Categorical clinical research centers		1,500		1,500		0
8. Total research grants	2,425	90,629	2,471	96,304	+46	+5,675

FELLOWSHIPS

	1967 estimate	1968 estimate	Increase or decrease
Fellowships	$6,129,000	$6,591,000	$462,000

INTRODUCTION

In the world of biomedical research today there is an increasing need for the maintenance of high standards of competence and for the enhancement of skills of the established investigator. Additionally, there is a strong need for highly specialized *de novo* training of postdoctoral non-medical investigators who future lies in "bench" research. The fellowship program is designed to stimulate and support training in specialized fields of biomedical research for Ph.D.'s in the fundamental disciplines and, in selected cases, for M.D.'s at particular sites where appropriate organized training programs do not exist. Fellowships also are used for retraining or updating of established investigators in newly developed or unique investigative techniques. Research Career Development Awards, an advanced form of fellowships, are utilized 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.

PROGRAM PLANS IN 1967 AND 1968

As in the case of the clinical training grants program, the basic problem which this program deals with is the dearth of qualified research investigators and teachers. The main limiting factor to more rapid expansion of the fellowship program is the number of eligible candidates.

The objectives of the Institute's program in this area is to expand the fellowships program so as to meet the growing need for highly qualified specialized manpower in the fundamental biomedical disciplines and clinical research areas.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	225	$3,513,000	231	$3,619,000	+6	+$106,000
(b) Competing	53	555,000	62	654,000	+9	+99,000
2. Supplementals	(4)	10,000	(4)	10,000	(—)	
3. New	206	2,051,000	215	2,308,000	+9	+257,000
4. Total fellowships	484	6,129,000	508	6,591,000	+24	+462,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Postdoctoral	215	$1,443,000	226	$1,669,000	+11	+$226,000
2. Special	107	1,215,000	115	1,325,000	+8	+110,000
3. Research career:						
(a) Career	31	817,000	31	817,000		
(b) Developmental	131	2,654,000	136	2,780,000	+5	+126,000
4. Total fellowships	484	6,129,000	508	6,591,000	+24	+462,000

TRAINING GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Training grants	$14,857,000	$15,706,000	+$849,000

INTRODUCTION

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.

PROGRAM PLANS IN 1967 AND 1968

At the present time, the overall training program is confronted with a demand situation unprecedented in scope. For example: about 25 new schools of medicine are being started or will be started in the next few years; in established medical schools new departments are being created as they respond to the current general broadening of the field of medicine and as they begin to meet the demands for improved teaching and research; and some of the existing schools which in the past did not place emphasis on research but attempted to produce medical practitioners, are now changing this emphasis toward production of more full-time educator-investigators in an effort to upgrade faculties. Thus, despite the success of Institute training programs in increasing the numbers of trained academic investigators in various specialties and disciplines, this added manpower is not only being fully absorbed but is in reality inadequate to meet expanding requirements. Further, the problem is compounded by the inordinate time required for developing qualified research investigators, particularly for the field of clinical investigation.

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 *special* experimental programs for training in clinical research investigation in a number of centers where innovations have been underway to explore new training approaches. With experience, the Institute plans to establish more such programs so as to produce clinical research investigators in their early, more imaginative and productive years. Current training grants are distributed among approximately 100 institutions, each having an average of three training grants. Growth in the number of institutions will be governed by (1) growth in the number of medical schools and (2) development of more biomedical research centers. The impact of the growth in the total number of institutions on demand for this type of support already is being felt.

Estimates of probable increases in the number of training grants *within* a single center are subject to greater uncertainties but a conservative judgment predicated on present trends within categorical areas warrants prediction of an increase in the average number of training programs per institutions from three to five in the next 10 years. The present Institute plan is based on expectation of an additional 10 institutions competing successfully for this type of support, and an average increase of one additional training grant per institution. Representative of this increase in the past five years has been the introduction of dermatology and orthopedics programs. Increases are expected in the areas of renal disease and urology and liver disease.

The following tables illustrate the estimated support of training by fields:

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	253	$11,961,000	258	$12,571,000	+5	+$610,000
(b) Competing	50	1,715,000	51	1,845,000	+1	+130,000
2. Supplementals	(17)	407,000	(18)	420,000	(+1)	+13,000
3. New	27	714,000	29	810,000	+2	+96,000
4. Scientific evaluation	(1)	60,000	(1)	60,000	(------)	----------
5. Total training grants	330	14,857,000	338	15,706,000	+8	+849,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Graduate	330	14,797,000	338	15,646,000	+8	+849,000
2. Scientific evaluation	(1)	60,000	(1)	60,000	--------	----------
3. Total training grants	330	14,857,000	338	15,706,000	+8	+849,000

Training grants program analysis

	1967 estimate	1968 estimate	Increase or decrease
Field:			
1. Arthritis	$1,750,000	$1,857,000	+$107,000
2. Dermatology	1,560,000	1,626,000	+66,000
3. Diabetes	705,000	749,000	+44,000
4. Endocrinology	1,725,000	1,801,000	+76,000
5. Metabolism	2,015,000	2,138,000	+123,000
6. Gastroenterology	2,120,000	2,250,000	+130,000
7. Hematology	2,040,000	2,165,000	+125,000
8. Nutrition	770,000	818,000	+48,000
9. Orthopedics	627,000	665,000	+38,000
10. Urology and kidney disease	825,000	876,000	+51,000
11. Experimental program	660,000	701,000	+41,000
12. Subtotal training grants	14,797,000	15,646,000	+849,000
13. Scientific evaluation	60,000	60,000	----------
14. Total training grants	14,857,000	15,706,000	+849,000

LABORATORY AND CLINICAL RESEARCH

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	531	$6,045,000	541	$6,233,000	+10	+$188,000
Other expenses	--------	7,203,000	--------	8,100,000	--------	+897,000
Total	531	13,248,000	541	14,333,000	+10	+1,085,000

INTRODUCTION

The intramural research program of the National Institute of Arthritis and Metabolic Diseases is engaged directly in laboratory and clinical investigations and studies into the etiology, diagnosis, treatment and prevention of a broad array of diseases notorious for their chronic nature and long-term disabling effects. Among them are arthritis and related rheumatic and connective tissue diseases, diabetes, cystic fibrosis and other inherited and acquired metabolic disorders, gastroenterological disorders, kidney and urological diseases, endocrine disorders, diseases of the blood and bone, and many others. Research also is conducted in such fields as orthopedic surgery, nutrition and dermatology.

The total program of intramural research also encompasses basic studies in the fundamental sciences associated with these diseases, such as chemistry, biochemistry, enzymology, molecular biology, anatomy, histology, pathology, physiology, medicinal chemistry, pharmacology, toxicology and genetics. These investigations are predicated in the theory that major progress in solving these health problems cannot be made without specific advances in the fundamental disciplines involved in each disease.

PROGRAM PLANS IN 1967 AND 1968

Arthritis and Rheumatism

Institute investigators this past year have conducted numerous clinical and laboratory studies aimed at further clarifying the causative factors involved in these diseases and at improving their diagnosis, prevention, methods of treatment, and management. Because of its crippling and disabling characteristics, considerable emphasis was again placed on the arthritic and related disease states, among them juvenile rheumatoid arthritis. Sjögren's syndrome, gout, rheumatoid arthritis, and Reiter's disease. In the past year numerous findings have been reported by Institute scientists that have shed new light on many of these debilitating disease conditions.

Of particular significance in this area was a study conducted jointly by Institute and NCI investigators which provides new information about certain cells which at times present problems in the differential diagnosis of rheumatoid arthritis. Their findings described a distinctive multinucleated synovial giant cell in rheumatoid arthritis. These cells were present in the knee joint synovia of nine out of 19 patients with active disease and positive serologic tests for rheumatoid arthritis. None were found in nine seronegative rheumatoid arthritis patients or in a series of control cases. The cells also were observed in joints other than the knee, and they could usually be readily distinguished from multinucleated plasma cells, foreign body giant cells and Touton cells which also occur frequently in rheumatoid arthritis.

Another finding provided important new knowledge about the development of joints. Contractions of the skeletal muscles, it has been suggested, may play a role in joint development during the embryonic stage. Previous studies of this theory, however, had failed to preserve the exact embryonic environment and, thus, the resulting deformities could not be attributed solely to the absence of movement. A study completed in the past year by scientists of the Institute and of National Institute of Child Health and Human Development now has shown that joints do not develop normally in chick embryos that have been paralyzed experimentally. Joint development abnormalities were found in chick embryos paralyzed by three different techniques. Joint cavities failed to develop and became filled with fibrous tissue that ultimately bound the joint elements together, and joint surfaces were flattened and distorted. These findings suggest that embryonic movement is essential for normal joint development, and may have important implications in the study of degenerative joint diseases such as osteoarthritis.

The Institute's very active clinical research program on gout has continued to produce new information about this disease. At the present time, gout can be the best controlled of all the arthritic diseases. Treatment aims at controlling excess uric acid accumulation in the body, and preventing or relieving the recurrent painful attacks. Potent drugs developed during the past decade (uricosuric drugs) are used to rid the body of its excess uric acid via the urine, thus preventing a built-up of harmful crystal deposits. These drugs, notably probenecid and

sulfin-pyrazone, are the mainstay of long-term maintenance treatment in gout. During the past year, Institute scientists have investigated the use of a newer drug, allopurinol, in gout patients. This drug, which blocks uric acid formation, is being studied in the management of patients who have not responded to other types of therapy.

Recent gout research at the Institute has also centered on the causes of high blood levels of uric acid in this disease, the way in which crystals of monosodium urate produce the inflammation of the acute attack of gouty arthritis, the mechanism for control of purine (the family of compounds of which uric acid is a member) synthesis, and the nature of the association of gout with other disorders such as glycogen storage disease.

In the most crippling of the arthritides, rheumatoid arthritis, the relatively gradual destruction of cartilage, bone, and supporting structures around the joints is ascribed to invasion of the structures by chronic inflammatory granulation tissue (pannus). Institute clinicians have been studying the effects of surgical removal of synovial tissue from the joints to prevent this progressive destruction. An intensive search is also being conducted for a possible causative microorganism in juvenile rheumatoid arthritis, which is characterized by joint inflammation beginning prior to the age of 14, and is accompanied by severe generalized evidence of disease.

Recent intramural studies of Reiter's syndrome have indicated that this disease, which is a triad of arthritis, inflammation of the urethra, and inflammation of the conjunctiva, is related to infection by a specific organism. A clinical study of pertinent responses related to the blood serum and immune mechanisms in young men with this disease is being conducted.

Sjögren's syndrome is a systemic disease which involves the salivary and tear-producing glands and may be associated with rheumatoid arthritis. Recent studies have revealed abnormal antibodies in the serum of patients with this syndrome, indicating that it may be a disorder of the body's immune system. Patients with Sjögren's syndrome and related disorders are participating in an extensive clinical investigation program at the Institute. Our investigators have observed that patients with apparently benign Sjögren's syndrome at the outset may develop malignant conditions of lymphoid tissue. This disease sequence has offered an opportunity to study the inter-relationship between benign and malignant diseases of the lymphoid and immune system.

Diabetes and Other Metabolic Diseases

Metabolism is an almost boundless research area which is being intensively studied by Institute scientists. Some of the diseases in this area are well known and frequent, while others are relatively rare. Of all the metabolic diseases, diabetes is probably the best known since it affects so many people.

A complex disease for which there is no known cure, diabetes ranks high on the list of fatal diseases. Diabetes research has passed through a recent phase in which significant advances have been made in therapy, notably development of the oral drugs for better blood sugar control of the older diabetic patient. It is now entering a phase in which studies of the more fundamental aspects, specific pathological tissue and molecular changes should lead ultimately to uncovering the cause of the disease.

In the past year, encouraging progress in fundamental and clinical studies of this inherited metabolic disorder has been reported by Institute investigators. For example, Institute scientists have elaborated further on the effect of hormones and other factors on the metabolism of fatty tissue in normal and diabetic animals. Further investigations provide hope to delineate the factors controlling the threshold of insulin action.

Two Institute scientists have recently investigated the role played by growth hormone, adrenocorticotropic hormone (ACTH), and the adrenal steroid hormones in the induction of diabetes in rats. Their findings indicate that growth hormone and ACTH play equally important roles and that each enhances the effect of the other. The present findings provide a better understanding of the complex hormonal interrelationships in diabetes, an area of research in which new information is accumulating rapidly.

In line with the Institute's research program in diabetes broad intensive and aggressive laboratory and clinical studies are slowly expanding our fundamental knowledge of this complex metabolic disorder and of the normal role of insulin. Bit by bit, new and illuminating information is gradually being shed on the factors which prevent insulin from doing its work efficiently and effectively in

the diabetic individual, what roles are individual, what roles are played by other hormones, and what factors are involved in the highly complex process by which glucose is transported from the blood to the interior of body cells.

Another metabolic disease of considerable interest to the Institute is cystic fibrosis, a grave, often fatal hereditary disease of childhood, adolescence, and young adulthood. The basic defect underlying cystic fibrosis is as yet unknown and much of the research carried on by Institute scientists in Bethesda is devoted to discovering the cause of this disorder. They are currently conducting laboratory and clinical studies in an attempt to delineate further the chemical and clinical manifestations of cystic fibrosis and to uncover the fundamental defect responsible for the disease. Trials are also being made to ascertain the best type of treatment for the chronic lung involvement which is the major cause of death. The relationship of this disorder to other types of chronic lung disease and gastrointestinal disorders is also being explored.

Homocystinuria is a relatively rare metabolic disease characterized chiefly by mental retardation. Two years ago several Institute scientists, in collaboration with investigators from the National Institute of Mental Health, determined the basic defect in this disease, the absence or lack of activity of a specific enzyme. The same group of scientists is continuing its studies of homocystinuria and a related disorder, cystathioninuria, in order to further explore the natural course of, and possible therapy for, these disorders.

Institute plans for the immediate future also provide for a specific new direction and expansion of intramural research in other inherited metabolic diseases via a program titled Chemical Physics that will emphasize studies affecting cellular metabolism, protein synthesis and enzyme action and regulation.

Endocrinology

The field of endocrinology encompasses an extremely wide spectrum of research problems, involving the internally secreting glands, such as the pituitary, thyroid and adrenal glands, and their respective roles in the physiology of the human body. To understand any disease process of physiologic disorder it is essential to consider the possible etiologic role of hormones secreted by these glands and the factors which regulate their synthesis, release and degradation. Institute research is pursuing intensively the isolation, purification, characterization and synthesis of hormones. Recent technical advances in biomedical research should aid immensely in elucidating the remaining unidentified factors.

One of the major roles of the pituitary gland hormones is to modify or regulate the size and functional activity of other glands or tissues, which in turn control the overall metabolic state of the individual. Certain metabolic abnormalities are corrected and some tumors beneficially affected by treatment with hormones or by removal of endocrine glands. Basic knowledge of the chemistry and physiology of pituitary protein hormones is limited.

Elucidation of the difference in structure of the pure hormone of different species will lead to a better understanding of the differences in biological activity and in antigenicity of a given hormone. This will shed light on the effects of excesses and deficiencies of these pituitary hormones, as well as allow for possible synthesis of hormones for therapeutic application.

Using pituitary glands of man and animals, Institute scientists are presently attempting to purify harmone preparations to develop and use sensitive qualitative and quantitative tests for estimation of their potency.

Studies are currently underway on patients with gigantism, or abnormal overgrowth, including specific assays for plasma growth hormone. Conversely, therapy with human growth hormone can dramatically increase the height and weight of pituitary dwarfs and more than double the growth rate in many instances. However, there is a severe shortage of human pituitaries collected for scientific purposes. Investigations underway are aimed at the possibility of modifying animal (bovine) growth hormone to make it effective in humans. Patients with tumors who appear to have excessive secretion of growth hormone, ACTH, TSH, vasopressin, or insulin are also under study.

A research finding of major significance in the field of endocrinology resulted from a study conducted by an Institute scientist of a Marshall Island population many years after it has been accidentally exposed to radioactive fallout in 1954. Pathologic changes were found in the thyroid gland in a number of the Marshallese, indicating that the seriousness of the internal hazard associated with fallout, particularly from radioiodine, must be revised upward and must be regarded as a major long-term hazard. The high incidence of thyroid ab-

normalities also emphasizes the caution with which radiation must be used clinically, particularly with children.

In another important study, an Institute scientist has found evidence of gonadotropin production by certain anaplastic large-cell carcinomas of the lung. Production of gonadotropins (a sex gland stimulating hormones), which normally is restricted to the pituitary gland and placenta, is ordinarily associated with endocrine tumors. This work describes the first documented instance of gonadotropic activity of non-endocrine tumors, specifically carcinomas of the lung.

The study involved four male smokers wtih breast enlargement (gynecomastia) and cancer and ten patients with cancer and no breast enlargement. Blood and urine as well as pituitary and lung tissue was examined for gonadotropic activity. Results of the study indicate that the source of gonadotropic activity in urine and blood of these patients was cancer of the lung. It is now clear that breast enlargement in an adult smoker demands careful evaluation and observation for carcinoma of the lung.

Another endocrine study is in progress on the nature of the hypothalamic-pituitary defect in the syndrome of hypogonadism (retardation of sexual development), due to a deficiency of pituitary gonadotropin, but with normal growth, thyroid function and adrenal function are also under careful endocrine and neurologic evaluation.

In the area of thyroid diseases, investigative studies are being conducted on patients with various types of goiter and thyroid nodules, abnomalities in thyroid hormone synthesis, goitrous hypothyroidism and hyperthyroidism. These various studies are providing additional information on the little understood workings and secretions of the endocrine system.

Kidney Disease

Diseases of the kidney and urinary tract also are of primary concern to the Institute. This past year, Institute scientists have reported numerous findings providing new insights into several diseases involving the kidneys. Of particular importance among these is cystinuria, a disease attributed to a heriditary defect in the ability to transport certain substances through the cells of renal tubules. It is characterized by urinary excretion of large amounts of the amino acids cystine, lysine, arginine and ornithine, and by the formation of cystine stones in the urinary tract. It has been suggested, however, that the disorder is due to more than one single inherited disease process. This past year, Institute investigators have obtained evidence of an intestinal, as well as a renal transport defect in this disorder. Their findings indicate that cystinuria encompasses at least three biochemically and genetically distinct defects.

In other investigations in this area, Institute scientists have found in clinical studies that allopurinol, a drug used in the treatment of gout, has potential use in patients with hyperuricemia (an excess of uric acid in the blood but not associated with gout) and renal insufficiency (a condition in which the kidneys are unable to remove a sufficient proportion of metabolic waste products). Intensive, continuing investigations also are being pursued by Institute researchers seeking to clarify the involvement of the kidneys in systemic lupus erythematosus (SLE), a grave inflammatory connective tissue disorder. The nature and severity of kidney involvement varies widely but when severe it is a common cause of death in this disorder.

Hematology

Diseases of the blood constitute a major public health problem and strike a considerable number of Americans. A detailed understanding of the blood and the many factors that affect it is an essential and invaluable requirement in the fight against blood disorders. Laboratory and clinical studies by Institute investigators this past year have made important contributions in furthering understanding of such blood diseases as hemophilia, pupura, the anemias, and many others.

Of particular importance to victims of hemophilia was the finding of an Institute scientist, in collaboration with an investigator in the National Institute of Dental Research, demonstrating that infusion of human anti-hemophilic globulin concentrate (AHG) is the best treatment available for hemophilic patients undergoing oral surgery who otherwise would run the risk of uncontrolled, life threatening hemorrhage. The investigators currently are evaluating less costly but equally effective plasma fractions for hemophilia

therapy. Their findings may also prove to have application in the treatment of other blood disorders in which hemorrhaging is a factor.

Meanwhile, continuing studies are being conducted by Institute investigators on the biochemistry of blood coagulation with particular reference to the development of better forms of therapy for various congenital and acquired hemorrhagic diseases. New approaches are being evaluated by Institute scientists to treatment of acute and chronic idiopathic thrombocytopenic purpura, a disease characterized by easy bruising and bleeding, and related conditions. Investigations also are being conducted in connection with the immunological aspects of various cytopenic states (conditions in which there are deficiencies in the cellular elements of the blood), which involve clinical studies of patients with thrombocytopenia, anemia or granulocytopenia caused by drug sensitivity.

The requested increase will provide for 5 positions and $78,000 for clinical investigations; 3 positions and $64,000 for additional efforts and support in chemical biology and physics; 2 positions and $23,000 for required assistance in scientific report writing; $195,000 for alterations and equipping of additional space to be provided through relocation of the NIH library; $67,000 for additional electronic computer services; $145,000 for selective strengthening of other developing programs through provision of required equipment, instrumentation, and supporting contractual services; $25,000 for annualization of positions new in 1967 offset by one less day of pay in 1968; and $479,000 for centrally furnished services form the National Institutes of Health management fund.

COLLABORATIVE RESEARCH AND DEVELOPMENT

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	25	$263,000	26	$279,000	+1	+$16,000
Other expenses		4,861,000		7,457,000		+2,596,000
Total	25	5,124,000	26	7,736,000	+1	+2,612,000

INTRODUCTION

This activity deals primarily with problems requiring the utilization of extra-Institute talent, resources, or facilities, usually through the contract mechanism, and often on a collaborative basis with other contractors and Institute personnel. The nature of research efforts so conducted are usually of a highly planned, specified-result, or developmental nature, but can also be fundamental if such work cannot be accomplished within the Institute's intramural research program. Another function of this activity is that of scientific communications including the publication of current-awareness journals and indexes, films, and other media of communications.

PROGRAM PLANS IN 1967 AND 1968

Current collaborative activities being pursued by this Institute include the following:

Artificial Kidney and Hemodialysis

Each year about 3,600 patients die of uremia, the end stage of kidney failure, who would be suitable for perpetual maintenance treatment with the aid of an artificial kidney. This unique and novel type of treatment has only become available in recent years after it had been developed largely with the support of research grants from this Institute. In order to make this lifesaving but highly expensive and complicated treatment available to as many patients as possible, this Institute initiated in 1966 a directed, mission-oriented and planned program of research and development in the artificial kidney field utilizing predominantly a direct contract approach. The artificial kidney program is aimed at obtaining via the shortest possible route a lowering of cost, and improvement in the effectiveness of artificial kidneys and related methods of dialysis, and improved rehabilitation of patients with end stage kidney failure.

Artificial kidneys are mechanical devices that can be used to cleanse the blood when the natural kidneys fail. Until permanently functioning transplantation of healthy kidneys from living or dead donors becomes a practical reality, blood purification through repeated use of an artificial kidney (chronic hemodialysis) is the only hope for survival for such patients.

While *some* patients in chronic kidney failure are being kept alive and productive through repeated treatment with the devices currently in use, *most* candidates for such treatment are unable to receive these benefits because of the cost and complexity of treatments.

Although artificial kidneys have been used for about two decades in cases of poisoning or acute kidney failure, their use on any one patient has been limited. Each time a patient required such a blood purifying apparatus, it was necessary to insert tubes into a major vein and artery to conduct blood from the patient through the artificial kidney and back into the patient's circulation. Each tube insertion often facilitated the onset of dangerous infections, and involved a new surgical procedure on a new pair of major blood vessels; thus, the number of times any one patient could be connected to an artificial kidney was limited. About five years ago, an Institute grantee developed use of permanently implanted, connected plastic tubes in an artery and vein of the forearm. The indwelling "shunt" makes it possible to connect a patient repeatedly to artificial kidneys without special surgical procedures and without the use and ultimate sacrifice of a new set of blood vessels with each dialysis. Development of this shunt started a new era of hemodialysis in patients with permanently impaired kidney function.

During the last few years it has been shown that the repeated routine use of artificial kidneys in such patients on a regular schedule would permit the saving of lives. Nevertheless, artificial kidney patients maintained with the aid of artificial kidneys still display a number of undesirable symptoms which may be related either to the basic chronic disease or to the treatment. Even so, using currently available techniques, the cost of hemodialysis both in terms of money and qualified manpower is extremely high. Moreover, authorities representing artificial kidney centers agree that improvements in hemodialysis must be based on additional knowledge of the nature of uremia. Such knowledge is as yet imperfect and must be developed side-by-side with effects to improve artificial kidney apparatus and techniques.

It was considered important to obtain for the Institute's Artificial Kidney Program, the best possible consultative talent from both outside and within the National Institutes of Health. Accordingly, 23 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.

A thorough study of the state of the art made it apparent that no single specific direction could be followed at present, 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 is being supported. Once it becomes evident that one or more approaches show greater promise, efforts will be concentrated in these directions.

The following are outstanding problems in dialysis and activities of highest priority toward which the new Artificial Kidney Program is directng immediate efforts:

1. Improvement of cannula materials, design and techniques so that current clotting and infection problems will be minimized. This involves redesign of cannula tips and bodies, development of a safer and simpler cannula coupling to the artificial kidney conduits, and the use of different cannula materials, including plastics permanently coated with anti-coagulants.

2. Development of improved or different membranes to permit a more selective and briefer dialysis. This involves the development and evaluation of tailor-make polymer membranes with controlled pore size and/or selective electrostatic properties, as well as mechanical modifications of the currently used cellulose sheeting and introduction of non-coagulating surface properties.

3. More efficient, less cumbersome and less costly dialyzer design. This involves the development of new disposable dialysis-ultrafiltration units, development of more compact dialyzers requiring less blood for priming, overall redesign of machines to simplify and shorten assembly and sterilization, introduction to artificial kidney design of plastic materials with non-coagulating surfaces, and expansion of two new concepts in artificial kidney dialysis; (a) "hollow fiber" kidneys, and (b) "diafiltration"—blood purification primarily through ultrafiltration, follow by artificial reconstitution of the filtrable blood solutes.

4. Improvement of operating efficiency and safety of large hospital dialysis centers and of home dialysis units. In hospital centers, this involves development of improved automatic central fluid delivery systems, and fail-safe monitoring systems for all aspects of dialysis (blood leakage, temperature, ionic concentrations of fluids). In home dialysis units, this involves inclusion of a fail-safe mechanism in event of accidental blood leakage—to permit unattended dialysis at night when patient and family are asleep.

5. High requirement for professional personnel. This requirement is based on the medical nature of dialysis, but aggravated by problems 1, 2, and 3 above.

6. Lack of effectiveness data. No objective information has been obtained through well-controlled studies which permits a meaningful evaluation of the comparative effectiveness of the various dialysis methods and equipment currently in use.

7. Undesirable symptoms frequently found in patients maintained by repeated dialysis:

a) Anemia. On the average, one or more blood transfusions are needed per month per patient maintained in dialysis—with the attendant high risk of transfusion hepatitis.

b) Peripheral neurological damage. This may be due to long-term effects of the semi-uremic state in surviving patients on repeated dialysis, or due to the dialysis procedure, *per se*.

c) Pseudo-gout, secondary hyperparathyroidism, skeletal demineralization, and calcium deposition in joints and in the tissues throughout the body. The most recent findings involve calcium deposition in the cornea of the eye. Simultaneously, there is a tendency to decalcification of bone with resultant fractures produced by minor stresses.

8. A systems analysis of the entire present chronic dialysis effort and of its methodologies and equipment. This includes a comparative evaluation of the various facets involved in chronic dialysis, from selection of the patient through his medical evaluation once he is being maintained with chronic dialysis. This includes a registry of all patients presently maintained with the aid of artificial kidneys or peritoneal dialysis. This overall systems analysis will continue as a longitudinal study of these patients and will be undertaken as a cooperative effort with the community service programs in dialysis of the National Center for Chronic Disease Control, 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.

Problems 1 through 4 are primarily responsible for the current high cost of dialysis, which averages $10,000–$14,000 per year in patients maintained by hospital dialysis on a twice-weekly schedule.

The Artificial Kidney-Chronic Uremia Program was mounted in record time with the activation of 24 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 major problems. These projects involve most of the developmental areas mentioned previously.

The portion of the program which is funded by extramural research grants complements closely the contract program described above, but is oriented more toward elucidation of clinical and fundamental biological problems related to the treatment of chronic uremia rather than toward hardware development.

The Institute convened an all-day workshop last November, attended by 27 researchers in the field, on standardization of hemodialysis membrane test methods which was instrumental in clarifying artificial kidney membrane development goals and in defining requirements of standardized tests and testing equipment. Several models of new equipment to test hemodialysis membranes were displayed during the workshop, two of which showed particular promise and were recommended for evaluation by third-party investigators.

Institute planning also is underway for a workshop on another phase of research in this area, the use of a special diet to decrease the need for intensified chronic dialysis.

Periodic optimistic stories in the lay press notwithstanding, the ultimate cheap, simple, efficient and safe artificial kidney for home use does not yet exist, nor does it loom in the immediate future. The program as outlined here is expected to close existing gaps systematically and to deal with treatment complications. Simultaneously, it introduces new engineering developments into the maintenance treatment of uremic patients and is expected to lead toward both better hardware and improved patient rehabilitation.

Scientific Communications

In today's complex world of science, the individual research scientist and physician face an almost insurmountable situation in keeping abreast of current advances described in the scientific literature published in his particular field of work. Aware of this need and of the existing communications gap, the Institute has sought to meet this challenge in its areas of responsibility by initiating a program of concise monthly current-awareness publications which make available to the scientist bibliographies and abstracts of all current scientific literature and papers most relevant to his special field of interest.

The first three such current awareness publications have successfully met this challenge and have been most enthusiastically received by the scientific community. These are: *Arthritis and Rheumatic Diseases Abstracts*, now in its second year of publication; *Diabetes Literature Index*, approaching its second year; and *Gastroenterology Abstracts and Citations*, completing its first year of publication. Their success and acceptance by the scientific community amply bears out the need for publications of this type.

At present, the Institute is starting publication of a new quarterly bibliography on chronic kidney failure, artificial kidneys, and dialysis methods as a useful current-awareness tool for facilitating better communication and greater integration of research and clinical efforts in this rapidly expanding field.

Institute planning currently is well underway in the development of several other current-awareness journals to fill existing scientific needs in the fields of endocrinology and nutrition. The Institute also is contemplating support of an annotated bibliography in cystic fibrosis, to be published by the National Cystic Fibrosis Research Foundation. In collaboration with the Foundation, the Institute has undertaken the production of a film on diagnosis and treatment of cystic fibrosis intended for widespread education of medical students, hospital staffs and practicing physicians.

National Pituitary Agency

The National Pituitary Agency has been established by the Institute for the collection of human pituitary glands and for the extraction and distribution of human growth hormone (HGH) for research and clinical studies by qualified investigators.

Human growth hormone, available only from human pituitary glands at the present time, functions primarily to regulate body growth processes. The demand for this hormone currently far exceeds the supply. It has been used effectively in treating hypopituitary dwarfism, and now clinical trials are being made in a variety of related disorders of delayed growth. Other research endeavors currently are seeking to derive a human growth stimulating function from bovine growth hormones through chemical modifications. Still other are seeking to synthesize HGH in the laboratory. Until it is synthesized, however, treatment on a large scale for hypopituitary dwarfism will not be possible.

In an effort to deal with this problem, the Institute is continuing its program of collection of pituitary glands from human cadavers and the systematic isolation and purification of pituitary gland hormones from this material, including HGH, through the National Pituitary Agency at Johns Hopkins Hospital in Baltimore. Through this agency investigators throughout the country are receiving the hormone for clinical trials and further research. An indication of the severity of the problem is illustrated by the fact that a single human pituitary gland yields only 3–5 mg of human growth hormone, sufficient for less than one week's experimental treatment of a hypopituitary or dwarfed child.

The requested increase will provide 1 position and $2,500,000 for continued development of the Artificial Kidney-Chronic Uremia program; $97,000 for additional current-awareness publications in the scientific communications program; $4,000 for annualization of positions new in 1967 offset by one less day of

pay in 1968; and $4,000 for centrally furnished services from the National Institutes of Health management fund.

BIOMETRY, EPIDEMIOLOGY AND FIELD STUDIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	26	$168,000	28	$186,000	+2	+$18,000
Other expenses		562,000		565,000		+3,000
Total	26	730,000	28	751,000	+2	+21,000

INTRODUCTION

In the continued search for new scientific knowledge, Institute scientists and clinicians are carrying out extensive field studies both of an epidemiological and clinical nature. These include studies of iodine metabolism, of the natural history of arthritis and rheumatism in American Indians, epidemiological and clinical studies of diabetes in certain American Indian tribes, and studies of gallbladder disease in selected American Indian tribes. The major portions of the population and clinical studies on arthritis and rheumatism, diabetes and gallbladders disease are carried out by the Institute's Clinical Field Studies Unit based in Phoenix, Arizona with a clinical component on the Gila River (Pima) Indian Reservation. This latter facility, a complete and portable structure connected to a wing of the Division of Indian Health hospital at Sacaton, Arizona, provides necessary laboratory and examination facilities for more intensive studies in these areas.

PROGRAM PLANS FOR 1967 AND 1968

Current objectives of the field projects of iodine metabolism include studies to determine the environmental factors that are associated with the prevalence of goiter and to examine more closely the nature of the metabolic defect responsible for the disease. Field studies carried out in two states have revealed that non-goitrous subjects appeared to be in negative iodine balance, i.e., iodine excretion exceeded iodine intake, whereas goitrous subjects appeared to be in positive iodine balance. A serious handicap to goiter investigators has been the lack of a reproducible method of estimating thyroid size. A satisfactory technique has been developed and validated and will be used in future studies which will be directed to verification of the relationship of goiter to water supply and to clinical and laboratory studies designed to identify the specific metabolic defect underlying goitrous conditions.

Thyroid studies on selected populations in Nevada and Arizona relating to the effects of radioactive substances in air, water and food will be continued.

Our field studies unit has found that the Pima Indians have the highest prevalence of diabetes ever recorded in an circumscribed population group—about 15 times the rate among the U.S. population as a whole. Population studies, such as this provide dependable new data, and since the disease is in part hereditary such studies can be accomplished more effectively among a stable, comparatively isolated group in which the forces of heredity may be observed more clearly than in a mobile population. Continuing studies among the Pimas in the past year by Institute scientists have now revealed that the effects of child bearing do not account for the higher prevalence of diabetes among women. Since the Pimas have large families in addition to a high prevalence of diabetes, data obtained was analyzed to test the hypotheses that increasing parity is associated with an increased risk of diabetes. These findings contradict findings of previous clinic studies by other investigators (in England) which lent support to a hypothesis that pregnancy precipitates frank diabetes in women genetically predisposed to the disorder. These studies will be continued and strengthened in order to evaluate the development and course of diabetes in this population. Studies will include diabetics, prediabetics and individuals who will not develop diabetes. Clinical studies will also be initiated to investigate the possibility of preventing or ameliorating the complications of the disease.

Included in the arthritis and rheumatism clinical field projects are studies to evaluate the development and progession of various forms of these conditions with particular emphasis on rheumatoid arthritis, ankylosing spondylitis and osteoarthrosis in the Pima Indians over a ten-year period; to investigate and evaluate various associated conditions and factors, including heredity, that may have a bearing on the frequency, severity and prognosis of arthritis and rheumatism in this population; and to contrast certain selected findings in the Pima Indian population with similar studies performed on other populations with different characteristics or environment.

The program increase of 2 positions and $9,000 will provide support for continuing these studies. Of the net increase requested, $6,000 is for annualization of positions new in 1967 and $6,000 is for centrally furnished services from the National Institutes of Health management fund.

REVIEW AND APPROVAL OF GRANTS

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	79	$678,000	81	$703,000	+2	+$25,000
Other expenses		1,246,000		1,454,000		+208,000
Total	79	1,924,000	81	2,157,000	+2	+233,000

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.

Due to sharply increasing costs in the conduct of biomedical research, competition for support of research proposals is far greater than has been experienced during the past several years. The average investment is high with a near corresponding decrease in numbers that can be funded. For this reason an increasing burden of awareness and of programs needs and continuing analyses in depth is required of the personnel engaged in this activity. Appraisals, and resultant advice, of required or desired investments to achieve or maintain program balance and most effective pursuit of research opportunities must be both timely and most professional.

The increase requested for this activity will provide two positions and $52,000 for their support and for increased electronic data processing costs; $4,000 for annualization of one new position in 1967; and $179,000 for centrally furnished services from the National Institutes of Health management fund. These increases are partially offset by a decrease of $2,000 for one less day of pay in 1968.

PROGRAM DIRECTION

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	22	$211,000	25	$248,000	+3	+$37,000
Other expenses		119,000		128,000		+9,000
Total	22	330,000	25	376,000	+3	+46,000

INTRODUCTION

This activity is comprised of the Institute Director, his immediate staff, and administrative management and service personnel. Responsibility lies herein for the general direction, coordination and administration of the total Institute activities.

The requested increase will provide three positions and $28,000 for required strengthening of management staff and for program analysis assistance, particularly with reference to in-depth studies relating to the programming and budgeting systems in the Institute. The request also includes $5,000 for annualization of one new position authorized in 1967, partially offset by a decrease of $1,000 for one less day of pay in 1968, and $14,000 for centrally furnished services from the National Institutes of Health management fund.

New positions requested in 1968

	Grade	Annual salary
Research:		
Scientist (3)	GS-16	$60,225
Science writer	GS-9	8,479
Do	GS-7	7,729
Research technician	GS-7	6,451
Secretary	GS-5	5,331
Clerk-stenographer	GS-3	4,269
Director grade	C.O.	19,261
Surgeon grade	C.O.	10,749
Collaborative research and development: Senior grade	C.O.	12,415
Biometry, epidemiology and field studies:		
Scientist	GS-11	9,536
Research technician	GS-5	6,387
Review and approval:		
Scientist	GS-13	12,873
Secretary	GS-6	5,867
Program direction:		
Senior medical officer	GS-17	22,760
Program analyst	GS-7	6,451
Clerk-stenographer	GS-4	4,776
Total, new positions, all activities (18)		203,559

TUESDAY, APRIL 11, 1967.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

WITNESSES

DR. RICHARD L. MASLAND, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

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

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. WILLIAM H. STEWART, SURGEON GENERAL

G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER

JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	5,348	5,647	5,830
11.3	Positions other than permanent	337	390	395
11.5	Other personnel compensation	88	95	102
	Total personnel compensation	5,773	6,132	6,327
12.0	Personnel benefits	518	547	560
21.0	Travel and transportation of persons	306	390	421
22.0	Transportation of things	98	122	132
23.0	Rent, communications, and utilities	186	213	235
24.0	Printing and reproduction	56	117	177
25.1	Other services	942	1,094	1,156
	Project contracts	1,535	3,494	3,950
25.3	Payment to "National Institutes of Health management fund"	5,171	5,428	6,218
26.0	Supplies and materials	1,083	1,184	1,487
31.0	Equipment	590	721	971
41.0	Grants, subsidies, and contributions	83,619	93,804	107,001
	Subtotal	99,877	113,246	128,635
95.0	Quarters and subsistence charges	−2	−2	−2
99.0	Total obligations	99,875	113,244	128,633

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	725	796	818
Full-time equivalent of other positions	45	60	60
Average number of all employees	693	795	813
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,934	$8,466

Program and financing

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Program by activities:			
	1. Grants:			
	(a) Research	62,907	71,496	84,416
	(b) Fellowships	3,093	3,675	3,805
	(c) Training	17,619	18,633	18,780
	Total grants	83,619	93,804	107,001
	2. Direct operations:			
	(a) Laboratory and clinical research	7,798	8,485	9,997
	(b) Collaborative research and development	3,554	5,565	5,980
	(c) Biometry, epidemiology, and field studies	1,650	2,268	2,305
	(d) Training	68	71	72
	(e) Review and approval of grants	1,777	2,180	2,389
	(f) Program direction	645	871	889
	Total direct operations	15,492	19,440	21,632
	Total program costs, funded [1]	99,111	113,244	128,633
	Change in selected resources [2]	764	----------	----------
10	Total obligations	99,875	113,244	128,633

See footnote at end of table.

Program and financing—Continued

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Financing:			
16 Comparative transfer to other accounts	366	558	
25 Unobligated balance lapsing	903	2,482	
New obligational authority	101,144	116,284	128,633
New obligational authority:			
40 Appropriation	101,153	116,296	128,633
41 Transferred to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−2		
"Operating expenses, Public Buildings Service," General Services Administration (79 Stat. 531 and 80 Stat. 674)	−7	−12	
43 Appropriation (adjusted)	101,144	116,284	128,633
Relation of obligations to expenditures:			
10 Total obligations	99,875	113,244	128,633
70 Receipts and other offsets (items 11 to 17)	366	558	
71 Obligations affecting expenditures	100,241	113,802	128,633
72 Obligated balance, start of year	43,067	64,824	81,093
74 Obligated balance, end of year	−64,824	−81,093	−106,853
77 Adjustments in expired accounts	−2,656		
90 Expenditures	75,828	97,533	102,873

[1] Includes capital outlay as follows: 1966, $378,000; 1967, $721,000; 1968, $971,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $1,027,000 (1966 adjustments, $1,000); 1966, $1,790,000; 1967, $1,790,000; 1968, $1,790,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. Now we have Dr. Richard L. Masland, Director of the National Institute of Neurological Diseases and Blindness. We have a biographical sketch of Dr. Masland here which we will insert in the record.

(The biographical sketch follows:)

Name: Masland, Richard L.
Position: Director, National Institute of Neurological Diseases and Blindness.
Birthplace and date: Philadelphia, Pa., March 24, 1910.
Education: A.B., Haverford College, 1931; M.D., University of Pennsylvania School of Medicine, 1935.
Experience:
1959: Director, National Institute of Neurological Diseases and Blindness.
1957–59: Assistant Director, NINDB.
1955–57: Professor, psychiatry and neurology (neurology), associate in physiology, 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: Am. Acad. of Neurology; Am. Neurological Assoc.; Assoc. for Research in Nervous and Mental Disorders; Am. Epilepsy Soc.; Am. EEG Soc.; Eastern EEG Soc.; Myasthenia Gravis Fnd.; The Assoc. for Research in Opthalmology (Honorary); Nat'l. Assoc. on Standard Med. Vo-

cabulary, honored consultant in the field of neurological diseases; Nat'l. MS Soc. Med. Adv. Bd.; Research to Prevent Blindness, Inc. Scient. Adv. Panel; Roscoe D. Jackson Mem. Lab., Bd. of Scient. Advisers; Easter Seal Research Fnd. Trustee; USP Research and Educational Fnd. Research Adv. Comm.; Muscular Dystrophy Assoc. of Am. Med. Adv. Bd.; Joseph P. Kennedy, Jr. Fund. Consultant, Member of Selection Comm. on Int. Achievement Awards Program in Mental Retardation; Montg. Co. Med. Soc. & Med. and Chirurgical Faculty, St. of Md.; Am. Pub. Health Assoc., VA Adv. Com. to P&N Service; Am. Heart Assoc., Coordinating Comm. 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; Award of Merit from Nat'l. Assoc. for Retarded Children, 1963; Myopia Research Fnd. Award, 1964; Nat'l. Multiple Sclerosis Society's Bronze Chest Award, 1964; N.Y. State Annual Mental Retardation Award, 1965; United Cerebral Palsy-Max Weinstein Award, 1967.

Mr. FLOOD. I see he had the good judgment to be born in Pennsylvania. You went to the old Quaker School at Haverford; an excellent school. Are you a Quaker by the way?

Dr. MASLAND. No, sir.

GENERAL STATEMENT

Mr. FLOOD. You have a statement, Doctor. I suppose you want to read that for us?

Dr. MASLAND. Yes, sir.

Federal programs for the care of the disabled are bringing to the attention of the public, now as never before, a problem which has long existed—the problem of the long-term care of the neurologically disabled. These include the victims of stroke, Parkinson's disease, multiple sclerosis, muscular dystrophy, epilepsy, cerebral palsy, brain tumors, head injury, paraplegia, and the many handicapping disorders of vision, speech, language, and hearing.

The economic burden of the neurologically disabled runs into billions of dollars annually; the human suffering of individuals and families is immeasurable. The ultimate solution must be prevention. For this reason, we urge that while the Government presses forward with programs of the rehabilitation and care of the disabled, continued support be given to the strong national research program for the elimination of these disorders.

ECONOMIC COST OF NEUROLOGICAL AND SENSORY DISORDERS

To appreciate the extent and long-term nature of these disabilities, it is helpful to review the records. About 200,000 adults are receiving social security benefits for lifetime disabilities which started in childhood. Of these, about 80 percent are victims of neurological disorders. Federal payments to this group alone cost the Government more than $10 million every month, yet this group represents but a small fraction of the total thus disabled, others being maintained by their families.

Another manifestation of neurological disease is becoming evident within the school system. Here we find that from 10 to 20 percent of the children are showing learning disabilities, often due to minimal brain dysfunction. In many instances, delay in speaking, inability to read, or school dropout are due to intellectual impairment from injury arising during pregnancy, or occurring at birth or during infantile illness or injury. In our complex society, this heavy burden of school failure and intellectual incompetence is intolerable.

Much more attention is now being given to the number of serious disabilities as well as deaths in an area affecting all ages—accidents. In 1965, more than 100,000 people were killed in accidents, half of which were automobile mishaps. Approximately 70 percent of these deaths from auto accidents resulted from head injury. Each year approximately 200,000 men, women, and children are hospitalized with some degree of head injury. Of these, nearly half are left with impairment which affects their future lives. In economic terms, the loss due to head injuries has been estimated as several billion dollars per year. Additionally, it is estimated that there may be as many as 60,000 paraplegics in the Nation needing various degrees of long-term care.

Major areas of neurological and sensory diseases in which parents need long-term care include blindness, deafness, stroke, Parkinson's disease, epilepsy, multiple sclerosis, brain tumor, and neuromusular disease. Over 400,000 are legally blind and more than a million are unable to read newsprints; 4 percent of the adult population suffers from serious hearing disabilities; some 2 million are presently disabled by stroke; 500,000 by Parkinson's disease; more than a million with epilepsy; 500,000 with multiple sclerosis and other demyelinating disorders; 200,000 have defects from brain tumors; and 250,000 with muscular dystrophy and other neuromuscular disorders.

For most of these disorders the cause is unknown, and no cure or effective treatment is available. The only hope for those now afflicted and for many others yet unborn is research.

EXAMPLES OF ECONOMIC GAINS FROM RESEARCH

The saving to the Nation through research accomplishment can readily be documented. An early example was prevention for a blinding eye disorder, retrolental fibroplasia (RLF). A study supported by NINDB established that this disorder resulted from excessive use of oxygen for babies born prematurely. Hospitals across the Nation were immediately alerted and within a year after the discovery, the number of babies blinded by RLF had decreased from several thousand a year to less than a dozen.

It is not possible to guess how quickly this important step would have been taken without the study developed by the Institute. However, for each year that this study advanced our knowledge, an estimated 1,860 infants were rescued from a lifetime of blindness. The lifetime care of these infants saved each year represents a saving to the Nation of approximately $130 million.

Eye research has brought many other significant advances in the past decade. A new antibiotic has proven effective in preventing blindness due to virus infection of the cornea. Sight for many has been restored through corneal transplants. Cataract surgery is now more generally available to the very young and the old than formerly. And glaucoma and retinal damage can be more accurately diagnosed and treated than in the past.

Research Opportunities

NEUROLOGICAL DISORDERS OF CHILDHOOD

At the present time a number of research opportunities are at hand for the Institute which could lead to similar advances. Within the

collaborative perinatal project, detailed pregnancy and obstetrical histories have now been recorded on over 60,000 women. The analyses of these data are serving to dramatize the importance of a number of previously suspected factors causing perinatal injury of the brain. The greatest single factor associated with birth defects appears to be prematurity. One of its important causes is incompetent cervix. Recent studies have shown that a relatively new surgical treatment for incompetent cervix has increased the neonatal survival rate and decreased fetal loss and neurological abnormality. As more attention is given to the potential of this comparatively simple surgical procedure, many birth defects should be avoided and many babies' lives saved.

Other research on the project has revealed a significant incidence of congenital toxoplasmosis (an infection of the newborn). Since a relationship to this infection and various abnormalities has been found, efforts are now being directed toward determining the mode of transmission of the infection and means for its prevention and treatment.

Mr. FLOOD. Where does it strike?

Dr. MASLAND. It affects the eye, leading to an inflammation of the retinal area. It can lead to blindness. It also invades the brain itself, causing areas of calcification scattered through the brain where little cystlike parasites are located. These irritate brain tissue and therefore patients with severe toxoplasmosis may exhibit epileptic seizures as well as mental deficiency.

DEGENERATIVE NEUROLOGICAL DISORDERS

One of the Institute's greatest research opportunities relates to slow and latent viruses as a possible cause of multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis. These viruses are called slow and latent because of their long incubation period. The program has been underway since 1962. This past year there was a significant research accomplishment—the transmission of a degenerative neurological disease of humans to laboratory animals. Kuru, a mysterious degenerative disease of people in New Guinea, was transmitted to chimpanzees. The condition bears some resemblance to multiple sclerosis and suggests that multiple sclerosis may have a similar basis.

The Institute's virus program is being conducted at a special laboratory established at Patuxent, Md., in cooperation with the Department of Interior's Fish and Wildlife Service. The major need for the development of this program is adequate animal-holding facilities. Space must be large enough to accommodate a number of animals of various species over a 5- to 10-year period following inoculation. These animals must be kept in isolation and free from contamination and in a manner which will not endanger the scientists conducting the research or the public.

HEAD INJURY

In response to the large national problem of death and disability resulting from head injury, the Institute has established a section on head injury to explore the nature of cerebral trauma, its management, treatment, incidence, and prevention. An Institute conference, sponsored by four of the major national societies, reviewed the field early in 1966, and many of the recommendations are being implemented.

To cope with the problem of head injury, much more needs to be known about where accidents occur, how persons are transported to hospital facilities, who is available to treat the patients, and how they are treated. In response to the directive of the Congress last year, specific clinical research centers are being established and others are being reorganized to take advantage of all current knowledge and apply it to the day-to-day problem of the head injury patient.

At the same time these clinical aspects of the problem are being studied, the Institute is moving forward with its Bethesda laboratory program of basic laboratory research on brain tissue reaction to head injury. This program includes studies of factors causing brain swelling and the reparative processes active in regrowth of tissue and restoration of function to the brain and spinal cord. Knowledge of the relationship between impact and physiological response will ultimately play a major role in determining the proper management and treatment of head injuries as well as aid in the development of more effective protective devices. The resources and collaboration of industry are also being utilized.

DISORDERS OF VISION

To provide a more effective national program to combat blindness, the Institute has taken important steps to mobilize a broad multidisciplinary attack. Eleven eye research centers are now being supported by the Institute. A National Information Center on Vision Research was established this year to disseminate scientific information and to aid in its analysis. The Institute's model reporting area for blindness statistics has now been extended to 14 States. And a special vision subcommittee of the Institute's National Advisory Council has been established to provide an overview of the Institute's vision program.

The most recent program development has been the establishment of eight outpatient units for vision research. Here, thousands of persons whose eye disorders do not require hospitalization can be studied in a more organized fashion by physician-scientists seeking clues to ocular disease.

The Institute has also proposed the creation of national eye care research institutes. Located initially in three or four diverse geographic areas, these would make possible the immediate application of research findings to individuals at the community level, and provide needed facilities for basic and clinical research.

STROKE

Stroke has been recognized by the Institute as a major health problem for many years and an extensive program of individual grants and research centers has been developed. At the present time there are 16 active centers located in major population centers of the country, and the Institute is prepared to increase and accelerate these activities as needed.

EPILEPSY

The Institute's program in epilepsy is built upon a broad base of individual research project grants and research projects within the Institute's laboratories at Bethesda. To provide focal points for a

broad, interdisciplinary attack on the problem, a number of clinical and basic research centers have been established. This year, a pilot project on the study of petit mal epilepsy was launched involving the cooperation of four extramural facilities. A standard therapeutic baseline for investigations into the control of seizures is sought.

The Institute is also working closely with the Advisory Committee on the Epilepsies appointed by the Surgeon General in the formulation of an overall plan for research in this area.

NEUROLOGICAL CONTROL

New techniques of neurological control hold exciting possibilities for the development of an artificial eye, a hearing device for the deaf, and means of movement control for the physically handicapped. To exploit computer techniques for a more sophisticated analysis of the nervous system and its functioning, a Laboratory of Neurological Control is planned by the Institute within its Bethesda program. This new program will be launched upon completion of NINDB's new laboratory building and selection of trained personnel to develop these new concepts.

EARLY RECOGNITION OF SENSORY DISORDERS

Another challenge for the Institute is the growing awareness of the need for early childhood recognition of speech, language, hearing, and vision problems, as well as possible minimal brain dysfunction. All present studies point to the need for these examinations to be conducted during the 3- to 5-year period in the life of the child, or earlier, in order that necessary therapy may be instituted and the child may be readied for a normal school environment.

Because of the need for effective therapy for the child with motor deficits, such as cerebral palsy, and because of the controversies present in this area, it may be necessary for the Institute to initiate a controlled study to evaluate available therapy.

To review the entire field of human communication, an Advisory Council Subcommittee was established in 1965. It has made a number of recommendations and will provide an extensive outline on needs by 1968.

TRAINING

To supply manpower for this continually evolving program, the Institute is now providing advanced research training for over 1,500 scientists.

The request for the National Institute of Neurological Diseases and Blindness for 1968 is $128,633,000, compared to the 1967 operating level of $113,244,000. The 1968 budget request contains increases of $15,389,000 including: $12,920,000 for research grants; $130,000 for research fellowships; $147,000 for training grants; $1,512,000 for direct research; $415,000 for collaborative research and development; $37,000 for biometry, epidemiology, and field studies; $1,000 for direct training; $209,000 for review and approval of grants; and $18,000 for program direction.

I shall be happy to answer any questions.

SUMMARY OF BUDGET REQUEST FOR NEUROLOGICAL DISEASES AND BLINDNESS

Mr. FLOOD. Now here comes this problem again. Your adjusted appropriation for 1967 is $115,726,000. The request for 1968 is $128,633,000. That is an increase of $12,907,000. Here is a strange one. This is the largest percentage increase we have come to. This is over 10 percent.

Dr. MASLAND. Yes.

UNOBLIGATED BALANCE RESERVED FOR SAVING

Mr. FLOOD. This would indicate you are pretty important, but in 1967 you have our old friend back again, the "Unobligated balance, reserve" of $2,482,000.

Dr. MASLAND. Yes, sir.

Mr. FLOOD. So you aren't considered so important in 1967, the current fiscal year.

Now, can you give us a logical explanation, why this big cut in 1967 and the big increase in 1968?

Dr. MASLAND. Yes, sir. I think Dr. Shannon has responded to this question in general. You will recall that the budget estimate was prepared many months in advance of these hearings.

Last year because of our great concern for the shortage of funds we accomplished——

Mr. FLOOD. Last year?

Dr. MASLAND. Yes, last year. We accomplished some additional savings in our grants program which we had not anticipated. These amounted to something over $2 million. These were in grants which were committed and which ordinarily are not reduced. In this particular program, the perinatal program, there have been some renegotiations. Parts of the program were cut back and a very considerable saving was accomplished. This is the primary basis of this rather large reserve.

OVERALL STATEMENT ON CALCULATION OF N.I.H. RESERVES

Dr. SHANNON. I think it will clarify the situation if I can take any one of the Institutes, or all of the Institutes, and show how the reserve is calculated, I think this would at least clarify it.

Mr. FLOOD. Give us a good, comprehensive statement covering all of N.I.H.

Dr. SHANNON. Yes.

(The statement was inadvertently omitted at this point and is included in the hearing record beginning at page 951.)

CONTINUATION OF EARLIER GRANTS

Mr. FLOOD. While this is a big increase compared to some of the other Institutes, practically all of the $11,835,000 is needed to finance a continuation of research projects started under grants made before 1968, and we have a moral commitment to finance them in 1968; is that about where we are?

Dr. MASLAND. Yes.

FELLOWSHIPS AND TRAINING

Mr. FLOOD. Most of the rest of your program seems to be going backward, especially in a shop like yours. I am surprised. New fellowship grants are down from 128 to 111. Not just the new grants, now, but training grants are down in total from 591 to 565, a decrease of 26. I cannot see why fellowships and training should not be going the other way.

Dr. SHANNON. The question is whether to support people already in research, who have ongoing programs, or to train more within the limited budget. I think the logical conclusion is that you support the people already there. This budget represents an example of the best one can do within a given ceiling and distribute it to get the best effect that one can in a very tight budget year.

Mr. FLOOD. Is that what you did here?

Dr. SHANNON. Yes. We have the choice under the overall dollar ceiling either to cut back on training or cut back on research. We feel we have a greater obligation to maintain the groups that are in being than to expand the training of new people. Now, again, this judgment is taken on the basis of the hope and expectation that such type budgets will not last for an indefinite period of time. So this is a short-range not a long-range judgment.

PUERTO RICO PROGRAMS

Mr. FLOOD. How are you doing in your Puerto Rico programs? That is more precise.

Dr. MASLAND. We have a very strong program now in Puerto Rico. We have five programs all of which we consider very important. Three are training programs and two are research. We are supporting two training programs in neurological sciences and we have an excellent training program for vision which is making a very signficant contribution. There are excellent people there and the program director is a most capable man.

LABORATORY OF PERINATAL PHYSIOLOGY

In research, we have a program relating to the properties of nerve fibers and their response to toxic agents. We also have an important research program in Puerto Rico in the perinatal research laboratory. This center is concentrating on development of the nervous system and on its disorders and on injuries of the brain during the perinatal period. That program to some extent parallels our collaborative perinatal project.

Mr. FLOOD. By perinatal you do not mean prenatal?

Dr. MASLAND. It includes the period just before birth, at the time of birth, and after. It is a more broadly encompassing term than prenatal but it includes the prenatal factors.

Mr. FLOOD. Yes, sir.

Dr. MASLAND. The laboratory in Puerto Rico permits us to explore in animals the problems which we observe in our clinical investigation of 60,000 women in our collaborative perinatal cooperative study.

We have now almost a thousand monkeys in Puerto Rico. We have a caged colony in the laboratory, and two island colonies where dis-

turbances of the animal behavior and neurological function can be observed in free-ranging environment.

We have now under investigation various methods whereby conditions such as mental retardation and cerebral palsy can be reproduced in monkeys and studied experimentally. These animal studies complement our clinical investigations which are limited to simple observation of the patient.

Mr. FLOOD. I wish you would expand that for the record.

Dr. MASLAND. Yes, sir.

Mr. FLOOD. This is a very interesting thing. Several people are interested in this.

Dr. MASLAND. I will be happy to do that, Mr. Chairman.

(The information follows:)

LABORATORY OF PERINATAL PHYSIOLOGY, PUERTO RICO

The Laboratory of Perinatal Physiology in Puerto Rico carries on studies in comparative neurology, physiological psychology, neurochemistry, and social behavior. The main focus of attention, however, is in the same cause and prevention of cerebral palsy and mental retardation. It has been possible to reproduce in monkeys almost all the classical pictures of cerebral palsy as it afflicts man.

The Institutes in Puerto Rico include a main laboratory at the U.S .Public Health Service Outpatient Clinic in San Juan, 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 built on the grounds of the Puerto Rico Medical Center, with completion expected in October 1969. In addition, steps are being taken to transfer near-by land from another federal agency and establish an experimental primate compound facility complementary to the new facility at the Medical Center.

The adjustments of the primate nervous system, and the reactions of damaged animals under more normal conditions are under investigation in free-ranging monkey colonies on several small off-shore islands. In addition to supporting scientific studies of the monkey, these facilities also provide a unique population of rhesus monkeys because of their known source of origin and their prolonged isolation from disease contact.

Detailed accounting of the pattern of reproductive activity and of birth on the islands of Cayo Santiago, La Cueva, and Guayacan has continued in an effort to characterize the pattern of cyclic reproduction as expressed in these three seqarate islands. Of particular importance is the fact that La Cueva and Guayacan share the same climatic and ecological environment although they remain entirely separate. The island of Cayo Santiago, located at the opposite end of Puerto Rico, represents a different environment, having an annual rainfall of 60 to 80 inches per year. This is in contrast to the dry, arid climate of La Cueva and Guayacan which enjoy only 20 inches of rain per year.

The seasons of reproductive activity and reproductive yields are settling down to a more stable pattern on a year by year basis in La Cueva and Guayacan as the monkey populations achieve a greater degree of stability. In the past year, the breeding and birth seasons on La Cueva and Guayacan have become closely similar in their timing and in the characteristics of their normal distribution. This is in contrast to the breeding and birth seasons on Cayo Santiago where the peaks of activity occurred three months earlier. Continuing statistics of this sort over the next three to five years will be required to determine more definitely the validity of the suggested proposition that breeding cyclicity in the primate may relate to environmental factors.

The addition of Desecheo as a facility for free-ranging monkey studies will add further dimensions to the analysis of the factors defining breeding periodicity. This island, approximately 600 acres in size, is of mountainous terrain and is covered with thick vegetation. It is currently being developed as a part of the primate ecology program. An integrated social group of approximately 70 monkeys has been transferred from Cayo Santiago to Desecheo. This group of monkeys was under intensive study on Cayo Santiago with reference to social organization, dominance hierarchy, and reproductive behavior. On Desecheo, this group again is being observed for changes in social structuring which may

result from the sudden transport of the group into an alien environment. Particular attention will be given to whether the group's integrity will be sustained or whether the group will fracture off into smaller subgroups. The reproductive periodicity and the dominance hierarchy will also be observed to ascertain possible effects of the disruption in life pattern brought about by the relocation.

Over the years, since its establishment, this laboratory has been in the forefront of studies concerned with normal and abnormal events surrounding the perinatal period. There are a number of recent accomplishments. Studies have been completed on the potential value of chemical analysis of amniotic fluid as an indicator of the fetal condition *in utero*. Studies of lactic acid levels, acidity, and bicarbonate concentration, and carbon dioxide levels during various stages of gestation, and under induced fetal distress have indicated that there is a serious delay in the changes of these values which limits the practical, clinical usefulness in emergency situations. Changes in these constituents were also observed during the administration of oxygen to the mother. Question has recently been raised as to whether the administration of oxygen during pregnancy might have harmful effects on the fetus. No evidence for this was obtained from these monkey experiments.

There has been a tendency to equate the size of the baby with the length of gestation. Small babies are quite properly generally considered premature. However, there is a special class of infants whose growth is retarded and who are actually small for their age. Such babies are spoken of as "small for dates." Studies have been carried out to determine whether this failure to grow in the uterus may reflect a disturbance of the uterine circulation. Experimental studies have clearly indicated the relationship between the extent of placental insufficiency, as produced by varying degrees of interference with circulation, and the degree of growth retardation exhibited in the offspring. Growth retardation at 45 percent has been exhibited by animals who have had ligation of the placental vessels. However, no relation has been found between the degree of growth retardation and the occurrence of minimal brain damage.

Another important cause of perinatal pathology in the human is *abruptio placentae*—the premature separation of the placenta from the uterine wall.

Experimentally produced abruption beyond 25 to 40 percent of its total volume results in immediate death of the fetus. Lesser degrees of abruption also have harmful effects, and these studies indicate that only minor degrees of redundancy of placental tissue exist in the monkey.

Asphyxia of the newborn has been considered a major cause of cerebral palsy and mental retardation. Previous studies have attempted to develop means for ameliorating the harmful effects. It has now been well established that period of asphyxia produces a reliable reproducible pattern of clinical and neuropathological change. Clinically, the animals exhibit profound sensory changes over the face and parts of the body. They show difficulty with sucking and swallowing, alterations in voice, and atoxic changes. Pathological examination of the brain reveals destruction of specific brain stem centers such as the sensory nucleus, the vestibular nuclei, the basal cerebellar nuclei, and certain other of the important ganglia of the brain. In spite of the reproducibility of this pattern, it is becoming evident that, in addition to the direct effects of asphyxia on the brain, secondary effects through changes in systemic blood pressure and alterations of the chemical constitutents of the circulation may also play a part.

Further studies utilizing asphyxia at term along with studies of blood pressure, heart rate, acid-base status, electrolyte distribution, lactate and other blood fractions are being carried out to determine the complex interaction of these elements in producing brain damage. An important incidental observation of these studies has shown that when Cesarean section is carried out under local anesthesia, the newborn monkey appears unusually vulnerable to the harmful effects of asphyxia. The possibility that anesthesia may actually have a protective effect is under investigation. Such studies in monkeys appear to be in conflict with observations in humans from the Collaborative Perinatal Study. In the Collaborative Study, when Cesarean section is performed under local anesthesia, the outcome appears more favorable than when a general anesthetic has been used.

Early work in the laboratory has indicated that the combination of perinatal asphyxia plus hyperbilirubinemia is required for the production of kernicterus. In spite of the fact that previous Institute-sponsored studies have affirmed the fact that kernicterus in humans can be markedly alleviated by exchange transfusion, crucial studies are still in progress to determine the mechanism through which the brain is injured in this condition and to search for less hazardous ways

for preventing this outcome. It has become clear, from studies in Puerto Rico, that the pattern of staining of the nuclei in the brain stem in experimental kernicterus in the monkey coincides with the pattern of neuropathological changes occurring in relation to asphyxiation at the time of birth. Present studies are extending these investigations in an attempt to produce animals with chronic neurological syndromes. These studies confirm the results of others that the presently proposed laboratory tests for bilirubin are poor indicators of the degree of hazard of the newborn child.

Studies in the Collaborative Perinatal Program are also indicating that, in many instances, it is fetal damage occurring in the early months of pregnancy which is responsible for cerebral palsy or mental retardation, rather than events immediately surrounding the birth process. Therefore, studies are in process in Puerto Rico with Rhesus Monkeys to obtain a clear picture of the nature of these unfavorable events of early pregnancy. Toward this end, techniques of fetal surgery have been developed so that the monkey fetus may be removed from the uterus, manipulated or injured in some way, and then returned to the uterus and carried forward to the usual delivery. Prolonged periods of compression of the umbilical cord are found to have surprisingly little harmful effect on the central nervous system of the newborn monkey. Compression for over 30 minutes may be required to produce brain damage. Efforts also have been made to produce pictures commonly spoken of as "hydranencephaly" as observed in human infants. Ligation of the major arteries of the brain has been carried out. Major vessel ligations are required to produce this picture.

Studies of harmful factors in the postnatal period of infancy are also in progress. It has been possible to reproduce both the clinical and neuropathological sequelae of lead intoxication in the newborn monkey. After lead ingestion, the animals developed irritability, anorexia, vomiting, convulsions, ataxia, and death. The pathogenesis of these changes is under investigation.

Studies are continued on the problem of experimental allergic encephalomyelitis as produced in the monkey. It has been found that the most susceptible age groups are the three to nine months old monkeys. After one year, the animals become less susceptible. The disease in infants is fulminating and associated with severe granulomatous, hemorrhagic, and even necrotizing reactions. An interesting aspect of the association of extensive hemorrhagic retinopathy. The retinal pattern closely resembles clinical conditions occasionally seen in the human.

These clinical investigations are being paralleled with experimental neuropathological studies of the brain changes occurring in the earliest stages of asphyxia. It is of particular importance to determine whether the results of asphyxia directly affect nerve cells, or whether these changes are mediated through some other structure such as the blood vessel or the glial cells.

An important National Conference on Brain Damage to the Fetus and Newborn—Effects of Acute or Chronic Hypoxia, held in Puerto Rico in January of this year, served to highlight the important recent advances taking place in this field and to which the Laboratory of Perinatal Physiology in Puerto Rico is making important contributions.

EPIDEMIOLOGY OF DEGENERATIVE DISEASES

Mr. FLOOD. You have given us some very interesting findings in the last 3 or 4 years on your work relative to epidemiology diseases.

Dr. MASLAND. Yes.

Mr. FLOOD. Is there anything new to report since last year?

Dr. MASLAND. Yes, sir. There is a group of diseases that are spoken of as degenerative diseases. It refers to the fact that a common factor in these diseases is an actual deterioration of the nerve tissue, a change in the structure of the brain cells and the nerve fibers, the cause of which is unknown. This includes conditions like Parkinsonism, multiple sclerosis, and a rather uncommon but very disabling disease called amytrophic lateral sclerosis. This is more popularly known as Lou Gehrig's disease because he died of this disease.

Mr. FLOOD. They are all progressive in their deterioration?

Dr. MASLAND. They are progressively disabling over long periods of time. The common factor is that we do not know the cause of any of them.

They have certain other common elements. One of the first approaches, then, in trying to uncover a cause is the epidemiological approach. For example, multiple sclerosis is one of this group. Our epidemiological investigations have disclosed that this is almost exclusively a disease of cold climates. It is very uncommon in the tropics.

Our most recent discovery is that it is more common in the favored socioeconomic groups. It is not common in the underprivileged groups.

The other intriguing thing is that whether you develop multiple sclerosis as an adult does not depend on who you are or where you are living as an adult; it depends on your background; it depends on where you were brought up. We have this information from the study of people who have developed multiple sclerosis in the Army. It did not depend upon where they were stationed; it depended on where they came from. There appears to be a latency here of as long as 5 or 10 years.

We know this from studies in Israel. People coming to Israel, where there is very little multiple sclerosis, people coming there from England, Scotland, or Scandinavia where there is a much higher incidence of the disease, show their first manifestation of multiple sclerosis 10 or 15 years after moving to Israel. This presents a real detective problem. What is it that could afflict a person in childhood but not manifest itself until 10 or 15 years later?

We believe that this may very well be some unusual latent virus. If it is a virus, it is very different from any yet discovered. The Kuru virus has a latency of 2 years, which is quite long.

Mr. FLOOD. Have you fellows abandoned bacteria? Do you no longer have problems with bacteria?

Dr. MASLAND. We still have a number of bacterial problems but I think these have been so well beaten down by antibiotics that they are not such a significant research problem in the nervous system.

Mr. FLOOD. They were extremely popular at one time.

Dr. MASLAND. I am not discounting bacteria. We have discovered in our perinatal studies that infantile meningitis due to bacteria is a not insignificant cause of mental deficiency. There are many babies whose brain is being damaged by bacterial infection in childhood.

This particular problem is not so much one of research as it is of service-management.

MYCOPLASMA

Mr. FLOOD. What is this new group coming along that is in between the two, something is popping up in between bacteria and virus?

Dr. SHANNON. Mycoplasma. In size, it is intermediate between the viruses and the bacteria; in functioning, in terms of its growth characteristics, it has certain elements of both. It is a class of organisms in its own right.

The reason I started to interrupt Dr. Masland is that you will hear the Allergy and Infectious Diseases Institute and I am sure they will point out that there are still bacterial problems, such as those in cholera, tuberculosis, veneral disease, diarrheal disease, meningitis.

Dr. MASLAND. Salmonella.

HEAD INJURIES

Mr. FLOOD. Do you think you have told us enough about head injuries?

Dr. MASLAND. I could submit some additional data for the record.

Mr. FLOOD. You decide that. I think you have done pretty well.

Dr. SHANNON. I would like to suggest what he might do: The head injury program is really run in conjunction with another program, in the Institute of General Medical Sciences, that deals with the general problems of trauma, whereas the Neurological Institute is dealing with the specialized problem of head injury. As the centers for the study of trauma evolve, some will have a general flavor, others will be related primarily to damage to the brain, but both elements of these programs would be carried together with a high degree of integration of the two programs.

Mr. FLOOD. I thought he covered it very well here today.

ANALYSIS OF DATA FROM PERINATAL STUDY

Are you placing greater emphasis on analysis of the data arising from the collaborative perinatal project?

Dr. MASLAND. Yes, sir. We are proceeding actively with these analyses. We have been very fortunate this year to have an expert committee of outstanding statisticians and epidemiologists whom we have brought in as consultants to provide guidance for the analysis of these data. The reports from the study should soon be forthcoming.

Mr. FLOOD. We will have those next year?

Dr. MASLAND. We should have.

SPECIAL DISEASE REPORTS

Mr. FLOOD. Will you please provide some information for the record on the following: Parkinson's disease, epilepsy, cerebral palsy, stroke, deafness, speech disorders, muscular distrophy, multiple sclerosis, nerve regeneration?

Dr. MASLAND. Yes, sir.

SPECIAL REPORT: PARKINSON'S DISEASE

THE PROBLEM

Parkinson's disease 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 prevalence along with the increase in average life span. Estimates of prevalence in the United States, vary, ranging from 500,000 to as high as 1,000,000. As to incidence, reports indicate that between 25,000 and 43,000 new cases develop each year.

Symptoms

First described in 1817 by James Parkinson, a London physician, the disorder affects the brain centers involved in the control and regulation of movement. The intellect, however, is ordinarily unimpaired. Due to disordered control of movement, rigidity of the muscles develops with uncontrollable trembling of the extremities, stooped posture, lethargy, loss of facial expression, and difficulty in walking, talking, writing, or any action requiring a high degree of muscular coordination.

Although the symptoms are usually progressive, and in most cases gradually produce disability and often complete helplessness, there are stationary periods

in some patients of 5, 10, or more years duration, during which there is little or no visible progression of the symptoms. Parkinson's disease is rarely the primary cause of death, but it may contribute to other causes.

Causes

The causes of Parkinson's disease are still unknown. In past years, epidemics of encephalitis, presumably due to a virus, have been responsible for many cases. However, since the last great epidemic in 1920 it is doubtful that this is a major current factor. Depletion of certain chemicals involved in nerve excitation, or selective degeneration of nerve cells producing these chemicals are other possible explanations. In all these conditions, the essential feature is destruction of nerve structures whose smooth functioning maintains a proper balance of control of movement.

Treatment

At present there is no specific treatment for Parkinson's disease, but drugs, physical therapy, and surgery offer three ways of alleviating the crippling symptoms. Drug therapy can accomplish a reduction of 25 to 50 percent of rigidity and tremor in most cases of Parkinsonism. Intensive physical therapy often can bring patients from 50 percent of normal to 75 percent, under ideal conditions. Surgery, although widely publicized, is of more limited use, because only 10 to 12 percent of all victims of Parkinson's disease are suitable subjects. Usually, patients over 65 are not helped by surgery. The improvements, however, that are possible under any of the three forms of treatment, or combination, are substantial, and provide encouragement to most patients.

THE INSTITUTE'S RESEARCH SPECTRUM

The Institute's research effort in Parkinson's disease includes the grant support of many individual projects in universities and other centers; the conduct of projects in its own laboratories in Bethesda, Maryland; the support of training in neurology, neurosurgery, neuropharmacology, and the many other disciplines bearing on the problem, and the development and coordination of a national program in the field.

INFORMATION AND RESEARCH CENTER

Information center

The Neurology Institute's major programming effort of the past few years has been the establishment and support of the Parkinson's Disease Information and Research Center at Columbia University is New York City. The Information Center, one part of the facility, is developing a comprehensive automated library service, including searching, evaluating, and computer storage and retrieval of the scientific literature on Parkinson's disease, and the publication of bibliographies, indexes, and critical reviews.

Some 30,000 items have been collected and indexed by the Center in its first 3 years of operation. A directory identifying research workers and describing current investigations throughout the world is being compiled. Most requests for information are now being routinely handled, and the Center will increase its services as the demand grows.

Clinical research

The Clinical Research Center, the other portion of the facility, is conducting a comprehensive research program aimed at determining the cause, improving diagnostic techniques, and developing methods of treatment of Parkinson's disease and related movement disorders. The program closely integrates basic and clinical research, and serves as a training center for research workers. Research Center scientists also serve the Information Center in an advisory and evaluative capacity.

Scientific review

Two of the primary tasks of the Center as a whole have been to survey the entire field of medical research as it relates to Parkinson's disease, and to bring together scientists from the various pertinent basic and clinical disciplines so that a strong concentration of interest could be created. The Center has produced the first review resulting from its survey, and will continue this activity on a periodic basis.

Conferences

The Center has conducted three large research 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 headed "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 on the function of the thalamus in converting sensory stimuli into physical movements, the biochemical mechanisms and imbalances underlying normal and defective metabolism of brain cells, and the physiology of nerve cells controlling movement.

Proceedings of the first two conferences have been published, and will be followed in 1967 by a volume recording the neurophysiology conference.

RESEARCH APPROACHES

Biochemistry

Due to advances in instrumentation and analytical methods, there is now greatly increased knowledge of some chemicals involved in the functioning of the brain. Deviations in the distribution and amount of certain of these chemicals has been observed in Parkinsonism. Especially because they appear to influence the excitability and activity of nervous structures involved in the control of voluntary movement, this finding is of great significance.

Specifically a group of chemical compounds known as biogenic amines, including dopamine-norepinephrine and serotonin, are found in high concentration around nerve endings at synapses in certain nuclear masses at the base of the brain (the basal ganglia). These compounds are believed to be involved in the process of excitation in these nuclei, which are directly involved in the control of movement. Drugs which interact with norepinephrine and serotonin may produce or ameliorate the symptoms of Parkinsonism. Postmortem analysis of the brains of patients dying with Parkinsonism reveals a specific reduction of dopamine in these structures. This reduction is not found in other neurological disorders, and appears to be specific for Parkinsonism. It is possible that some forms of Parkinsonism are due to this deficiency.

Several compounds called enzymes, including DOPA decarboxylase and monamine oxidase, are essential in the synthesis and breakdown of these biogenic amines. Their activity in the basal ganglia of Parkinson patients is of special interest. Compounds have been discovered that inhibit the various enzymatic reactions in both animals and man. Some of these compounds have been reported to relieve Parkinsonlike symptoms artificially induced in animals by drugs.

Trials of enzyme inhibitors in Parkinson's disease patients have not yet produced any conclusive positive results; however, these compounds have provided a valuable new approach to the overall understanding of basal ganglia metabolism.

Also much reduced in the basal ganglia of patients with Parkinson's disease is the pigment melanin, which normally gives a dark color to the area of the brain known as the substantia nigra. Loss of melanin is the most common finding in postmortem Parkinsonism tissue studies.

Institute grantees at the Columbia Center are conducting extensive cytochemical and electron microscope studies of this pigment, its distribution throughout the nervous system, and differences in its ultrastructure observed in tissues from Parkinsonism patients. Other National Institutes of Health grantees, working in collaboration with intramural scientists, have reported evidence this year that the melanin present in brain tissue has a fine structure chemical composition, and mode of formation distinctly different from the melanin in skin and other body tissues, and should be separately classified.

Structure and function of the nervous system

The disordered movements of Parkinsonism reflect a disorder of functioning of those structures within the brain which are involved in voluntary movement and its control. The study of these mechanisms and their disorders is thus of the utmost importance in Parkinsonism. Technical advances are continually improving our ability to study the activity of the nerves in the brain and the anatomical pathways through which the control of movement is affected. In animals, surgical lesions may be produced in discrete areas and the deficits which result evaluated. In man and animals, newly developed microelectrodes—

hairlike tungsten or stainless steel probes planted deep within the brain—are being used to record the spontaneous and evoked activity within various brain structures. Deviations in this activity in patients with Parkinsonism have been observed. Such studies are providing information regarding the structures involved in normal and disordered movement and the functional derangements which result from injuries of these structures.

Scientists working with such microelectrodes implanted within brain structures are also studying the possibility of simultaneous use of fine catheters for the introduction of various drugs which act upon synapses (nerve junctions). Such procedures would permit greater accuracy in determining the sites of action of drugs of proven therapeutic value, and would provide valuable information on the chemistry of the synaptic organizations involved in movement disorders.

The application of surgery to the treatment of Parkinsonism incidentally rendered many structures and areas newly accessible for study in concert with treatment. Tiny amounts of nerve cell tissue removed from Parkinsonism patients during surgery are available for electron-microscopic and other studies of ultrastructure and function.

Theory of Movement Control

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. This 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 of the biogenic-amine pathway. Symptoms may be alleviated by accomplishing a corresponding reduction in activity in the parallel acetylcholine mediated system. In practice, this can be accompilshed by drugs, or in some instances by surgery.

Therapy

Drugs.—Until the underlying causes of Parkinson's disease are discovered, treatment must necessarily be concentrated on control of symptoms. Because a number of symptoms are involved, and their relative severity varies widely, medication must be tailored to the needs and tolerance of each patient on an individual basis.

Many good drugs are now available to the physician, each influencing a certain symptom or set of symptoms. Naturally occurring drugs of plant origin have been replaced in the past 10 years by synthetics which control involuntary muscle spasms and termors, block the passage of nerve impulses to the motor muscles, and reduce rigidity. New studies are directed more specifically to the interaction of new drugs and enzymes with the naturally occurring biogenic amines of the brain.

A comprehensive review of the literature on drug therapy for Parkinson's disease has been prepared by Institute grantees, and will be published in 1967.

Surgery.—The second approach to the restoration of balance between the two systems is by partial surgical interruption of the overactive pathway. Institute scientists and grantees continue to develop refinements in the methods of producing the necessary tiny lesions in the thalamus, which now include simple cutting, electrocoagulation, freezing, injection of chemical agents, and ultrasound.

An important recent development in surgery for Parkinson's disease has been the use of electroprobes. These are tiny electrodes placed within the brain and moved slightly until electrical impulses picked up correspond precisely with arm or hand movements. The exact source of the tremor may thus be pinpointed, greatly increasing the accuracy of the surgery.

Epidemiology

Better epidemiological data on Parkinson's disease are the aim of several Institute-supported projects. A study published this year of vital statistics records in England and Wales from 1855 to 1962 brought out a number of significant findings about Parkinson's disease. (These records were chosen because they use the most consistent terminology, contain the most extensive data, and cover a longer period than any others in the world.) The study shows a small increase of paralysis agitans in ages 65 to 74 and a more striking increase in individuals dying after the age of 75. There are also indications of a small increase of paralysis agitans mortality during the period 1926 to 1940—the period during

which the Parkinson's sequelae of von Economo's encephalitis reached their greatest prominence.

Another epidemiological study including Parkinson's disease is being conducted among the Chamorro population of Guam. Chamorrans have an extremely high rate of Parkinsonism associated with dementia, and also associated with amyotrophic lateral sclerosis, a disease involving degeneration of motor cells in the spinal cord. Genetic trails, din, and electron examination of autopsy material are among the approaches being taken in this study.

Viral studies

Although there has been no recent epidemic of Parkinson-producing encephalitis since the 1920's, it is possible that sporadic cases are still due to an infectious agent. Such an infectious agent, which may have been a virus, was never detected. It is uncertain whether this infection or other agents are continuing to play a part in producing Parkinson's disease; however, many viruses that are known to destroy nerve tissues gradually and cause death after years of latent infection are being grown and studied in test tubes and in animals at an institute laboratory. Efforts are also being made to culture viruses from patients with Parkinson's disease whose symptoms resemble those of chronic encephalitis.

OUTLOOK

Cause and cure of Parkinson's disease remain unknown. However, much can be done to control its symptoms; highly encouraging research in in progress in a number of medical centers. The Institute is supporting much of this research, and there is every reason to expect the program to continue to gain in size, strength, and accomplishment. Research 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.

SPECIAL REPORT EPILEPSY

INTRODUCTION

The convulsive disorders (epilepsy) affect an estimated one to two million Americans of all ages. The prevalence is higher in children than in adults.

Epilepsy has many manifestations. Minor seizures may appear as momentary lapses of consciousness (petit mal)—frequently unrecognized as seizures except by the trained observer. Psychomotor seizures cause transitory episodes of distorted perception or behavior. Partial (focal) seizures cause localized sensations or convulsive movements. The most severe (grand mal) are those causing generalized convulsions and profound unconsciousness.

Scientific opinion differs on the fundamental cause or causes of the disorder. Epilepsy not infrequently results from injury or disease of the brain. However, in other instances, no such cause is evident.

Some physicians hold that all forms of epilepsy, including both the generalized (grand mal and petit mal) and the localized (psychomotor and focal) are a single disease entity with a common fundamental causative factor. Others believe that although certain mechanisms of neuronal discharge are operative in all cases, the causative chemical, anatomical, or functional defect may differ widely in different types of cases.

At the present time, physicians can control (but not cure) seizures in the majority of epilepsy patients by giving them anticonvulsant drugs. The recording of the electrical activity of the brain (electroencephalogram—EEG) is a widely used means for diagnosis and study of the disorder.

The National Institute of Neurological Diseases and Blindness' (NINDB) research program in epilepsy is designed to learn more of the factors causing the disorder (genetic, traumatic, infectious, biochemical, and socio-environmental); the factors precipitating seizures; and treatment, both medical and surgical.

PROGRAM DEVELOPMENT

The Institute's program is focused on the development of a more refined classification of the epilepsies, better techniques for differentiating various types, deeper knowledge of the fundamental mechanisms of nerve activity underlying the seizure, and more effective procedures for prevention and therapy. The program is built upon a broad base of individual research project grants to scientists

representing many disciplines in laboratories throughout the United States and overseas, and it includes projects within the Institute's laboratories at Bethesda. To provide focal points for a broad, interdisciplinary attack on the problem, a number of clinical and basic research centers have been established.

In addition, Institute scientists are coordinating the activities of a number of research centers in organized national programs. These programs, directed toward the intensive investigation of groups of epileptic patients and toward the development and testing of anticonvulsant drugs, may involve both university scientists and the pharmaceutical industry.

Four major clinical research centers in epilepsy have been established. One is located at the University of Washington where studies of the fundamental mechanisms underlying epilepsy are being conducted by a multidisciplinary research team. The disciplines of neurological surgery, electroencephalography, neurophysiology, neuroanatomy, behavioral physiology, and neuropharmacology are represented in this many-faceted approach to epilepsy. In addition, the center has established a Seizure Clinic where epilepsy patients may be studied and treated. A variety of seizure-associated clinical problems to be explored include: studies of the natural history of epilepsy, evaluation of anticonvulsant drugs, studies of the physiological mechanisms underlying seizures, studies of the effects of certain drugs on seizure mechanisms, the role of environmental stress in the precipitation of seizures, the effects of systemic metabolic disturbances on seizure thresholds, and an examination of the genetic patterns of epilepsy.

The epilepsy center at the University of Wisconsin also is conducting both clinical and basic research studies. Basic neurochemistry studies are now in progress on seizures induced by vitamin B_6 deficiency in laboratory animals. In the area of clinical research, genetic studies are being conducted with families having a history of epilepsy and with a group of school-age twins; new anticonvulsant drugs are being tested; neuropsychological investigations are evaluating intellectual and adaptive functions in epilepsy patients; and conditioning studies are under way on patients who have photosensitive, musicogenic, sound-induced, and pattern-evoked seizures.

A third center at the Brain Research Institute, University of California at Los Angeles, is concentrating on a study of the electrical processes underlying the epileptic state in animals and in man. Clinical studies at this center have been primarily concerned with temporal lobe epilepsy patients. Some of these patients have undergone surgery to alleviate seizures, and investigations have included evaluation of the beneficial effects of surgery in these cases as well as anatomical and pathological studies of the temporal lobes removed.

This year, the Institute initiated support for an epilepsy research center at Yale University where physicians are studying basic mechanisms of epileptic discharges in animals.

A study at the Neuropharmacology Research Center of the University of Utah is primarily concerned with the mechanism of action of anticonvulsants. An Institute-supported panel is continuing to evaluate methods of testing anticonvulsant agents. Specific problems of testing methods are being clarified prior to commencing the broad testing of anticonvulsants.

Computer centers for EEG analysis are a relatively new aspect of epilepsy research. The development of more sensitive amplifiers has made possible the better understanding of the essential nature of the electrical nerve discharge, and the recording of the electrical changes which accompany nerve activity. Computer techniques, which permit sophisticated and high-speed mathematical analysis of massive amounts of data from EEG recordings, make this information more meaningful. The Institute has supported an EEG-computer laboratory in Paris, which was the early pioneer in the use of these techniques and has aided in the development of a computer center for neurological research at the University of California at Los Angeles.

International research on epilspey combines the special research knowledge and skills of scientists at several universities, both here and abroad. One relationship involves the University of Wisconsin and the Institute of Brain Research, Zurich, Switzerland. At these two centers, experts are studying the effects of conditioning on brain function. Other international research efforts are concerned with disturbed consciousness in epilepsy patients.

The Institute's newly launched collaborative study of epilepsy includes a pilot project seeking a standard therapeutic baseline for investigations into the control of seizures. Four medical centers—Marquette University, the University of Virginia, Montreal Children's Hospital, and the Tufts-New England Medical Cen-

ter—are developing a network of units for this initial phase of the study. In the interest of uniformity, only one anticonvulsant, ethosuximide, is being used in the first 2-year portion of this program. Only one type of epilepsy—petit mal or loss-of-consciousness seizures—will be studied. This type occurs most often in children and adolescents.

In the Institute's clinical research program at Bethesda, as well as at Institute-supported centers, physicians also are conducting studies to determine the relationship of head injuries to the development of epilepsy, and are evaluating advanced surgical techniques and instrumentation with selected epilepsy patients.

Two important committees now provide guidance in the Nation's efforts against the epilepsies. In April 1965, the Department of Health, Education, and Welfare formed a Departmental Committee on Epilepsy with representatives from the Office of Education, Vocational Rehabilitation Administration, the Welfare Administraiton, and the Public Health Service. This committee keeps participating agencies apprised of current activities in epilepsy, prevents duplication, and encourages coordinated activities.

Also, the Surgeon General of the Public Health Service appointed an Advisory Committee on the Epilepsies this year to recommend action at the national level for the prevention and control of the epilepsies. The Committee consists of two subcommittees: one for service, the other for research. The Chairman of the full Committee is a former member of NINDB's National Advisory Council, and the Committee's Executive Secretary is an Associate Director of the Institute. Useful to the Committee in considering both research and service needs is the Institute's Monograph No. 1, "Epilepsy: A Review of Basic and Clinical Research," published this year, as well as the proceedings of an Institute-sponsored conference on "Neurological and Electroencephalographic Correlation Studies in Infancy."

RESEARCH ACCOMPLISHMENTS

Because the activity of nerve cells often becomes distorted in epilepsy and other brain disorders, the Institute is supporting research designed to clarify the form, structure, chemistry, and functioning of normal brain tissue. Such studies are providing data necessary for understanding the changes in the brain which cause or are caused by seizures.

Scientists are inducing epilepsy in experimental animals by electrical or chemical stimulation of a point on the brain's surface. This stimulation causes an irritative, seizure-producing focus. In one study, methionine sulfoximine (MSO) has produced seizures in animals that closely approximate clinical epilepsy in man. These seizures occur spontaneously and repetitively in experimental animals approximately 24 hours after they receive the compound. Chemical studies of brain tissue from these animals show alterations in the level of glutamine, a normally occurring constituent whose activities may relate to seizure susceptibility of the brain.

The development of a focus of epileptic tissue in one area of the brain may lead to the formation of a secondary focus in another area. Recording this electrical storm as it spreads throughout the brain verifies the formation of secondary foci. Studies of nerve cells within these foci have been designed to pinpoint the structural and chemical changes which occur in the epileptic brain cells.

A microtechnique for applying a chemical compound to a single neuron in the brain has been developed. With this technique, it is possible also to monitor the neuron at the time it is receiving the compound to note any changes that may occur. Certain compounds have been used to produce seizure activity in a single neuron in the brain of a laboratory animal. Following this, various substances have been tested for effectiveness in halting the abnormal activity. Results of these tests show that the application of control substances does not appear to be effective in arresting seizure activity and that seizure activity is a "spreading" phenomenon. It may spread from the single treated neuron to other untreated ones and result in a generalized seizure in the animal.

Scientists also have been concerned with the effects of sodium and potassium salt concentrations on brain cells. One researcher has observed the effects of varying concentrations of these salts placed in the ventricle of an animal's brain. By monitoring the brain's electrical activity after the salt solution was injected, he demonstrated that an increase in salt concentration, independent of the volume of solution applied, would produce a seizure.

In some patients, seizures are induced by sensory stimuli such as a flash of light, an unusual sound, or even certain types of music. In a clinical study,

patients with sensory-evoked epilepsy were taught to tolerate the noxious stimuli by a conditioning process. A computer automation program was devised which would present the stimulus—which might be a certain musical composition, a startling noise, or a type of light—in combination with a similar but benign stimulus or at a benign frequency. When the patients became insensitive to the stimuli activity (seizure was no longer produced by it), they were taught to reinforce the conditioning to maintain their own insensitivity. Physicians working with these patients were afforded the opportunity to study one of the rarer forms of epilepsy and to develop an effective treatment, if not a cure, for it.

FUTURE PLANS

Following the recommendations of the PHS Advisory Committee on the Epilepsies, the Institute is expanding its epilepsy programs. Support now is being extended for epidemiologic studies, which will better identify the magnitude and complexity of this problem as well as provide an indication of future research needs.

Consideration is being given to the formation of an "epilepsy information center" which would provide a critical appraisal of the current field of knowledge and a method for the collection, storage, retrieval, and dissemination of medical data on the epilepsies.

A special effort currently is being made to encourage the production and testing of new anticonvulsant drugs. Twenty-nine drug firms have been surveyed for new drugs which have not yet been marketed and have been asked to cooperate in the development of ways whereby these can be brought promptly to clinical evaluation. A parallel survey has been made of university pharmacology departments to encourage their scientists to assist in research on the mode of action of anticonvulsants and in the training of neuropharmacologists.

Because a number of patients suffering from epilepsy cannot be controlled by anticonvulsants now available, the search for more efficacious compounds must continue. In addition, drugs with the same effectiveness as those currently in use, but which produce fewer or less serious side effects, are needed.

A visiting consultant to the Director has recently completed an in-depth analysis and evaluation of the nationwide research programs in neurochemistry as applied to epilepsy. Similar analyses and evaluations will be undertaken in the field of neuropharmacology and other areas of basic research.

Expansion of the collaborative study of epilepsy is planned. While the pilot study progresses, plans are being made for an expeditious transition to long-range programs.

SPECIAL REPORT: CEREBRAL PALSY

THE PROBLEM

Cerebral palsy is a broad term used to describe a variety of chronic conditions in which brain damage, usually occurring at birth, impairs motor function. Cerebral palsy (CP) affects about 6 of every 1,000 liveborn infants.

Symptoms in CP may range from mild muscle incoordination to more severe physical handicaps. Impairments of motor function may involve upper or lower extremities, or both, and may affect one or both sides of the body.

Although the primary symptom in cerebral palsy is motor damage, there may or may not be other manifestations of brain damage. However, most cerebral palsied individuals show destruction of brain tissue.

The two most predominant types of the disorder are the spastic form and the athetold type. The former is characterized by tense contracted muscle, while the primary symptom of the latter is involuntary and uncontrolled movements of arms and legs.

Within the constellatien of associated disabilities that may occur in CP are intellectual impairment, convulsive seizures, speech defects, disorders of vision and hearings, and certain other brain-centered disorders, including specific learning difficulties and behavioral abnormalities.

Neurological or sensory signs of the child's abnormal development are sometimes detected at birth but in other instances do not become apparent until months or even several years later. Early detection and diagnosis of CP in the infant or young child is crucially important in helping to prevent or lessen the extent of the handicapping effects of the disorder.

CAUSES

The different forms of cerebral palsy are rooted in multiple causes of injury or disease of brain tissue, many of which are essentially unknown or only suspected. Some of the causes of CP occurring in the period before, during, and after birth have been identified or implicated:

Chronic or acute anoxia (oxygen deprivation) is one of the leading factors known to precede the condition of CP and other serious neurological disorders of childhood.

Rubella (German measles), contracted by the expectant mother early in pregnancy, can do serious damage to the developing nervous system of the fetus.

Obstetrical complications, such as breech birth and twin delivery, can figure in the cause of CP.

Prematurity is strongly associated with CP. The premature infant, particularly of low birth weight, is susceptible to asphyxia from respiratory distress. (Asphyxia implies not only oxygen lack but also excess carbon dioxide and other changes in blood and metabolic processes.)

Jaundice of the newborn may produce an illness called kernicterus, in which mild or severe damage of the central nervous system may occur. Most cases of kernicterus are due to incompatibility of the red blood-cell Rh factor between the developing fetus and the mother, or other blood-type conflict.

Toxemia of pregancy, maternal diabetes, and other maternal illnesses are predisposing factors to CP in the developing fetus.

Postnatal infection, such as encephalitis or meningitis during infancy or early childhood, may produce symptoms of cerebral palsy.

The search for other causes and preventives must go on. Whatever the causes, a paramount obligation of the present is to enable every infant or young child diagnosed with cerebral palsy to receive the benefit of specialized programs of therapy, management, and education.

THE RESEARCH SPECTRUM

Because of its diffuse causes, cerebral palsy takes in a wide research spectrum. Each of its many different origins must first be identified and controlled before the multitude of conditions known as "cerebral palsy" can be overcome. Simultaneously with discovering and conquering the conditions responsible for CP, methods must be developed to train and treat those who now have the disorder to utilize their remaining motor skills. Both objectives—finding causes and preventives and developing effective treatments—remain an undiminished challenge to the National Institute of Neurological Diseases and Blindness.

Even if the causes of CP were soon eliminated, many people in the country who already suffer the effects of destruction of important elements of the central nervous system will continue to need help in overcoming their handicaps. In order to understand and develop the best methods for retraining a damaged brain to compensate for lost function, scientists must acquire complete knowledge of the intricacies of that master organ.

Thus, research in brain damage ranges from conducting fundamental research on how the brain funtcions, how movements are initiated by the brain and integrated into smooth rhythmic actions, as opposed to the awkward, ineffective motions of the brain-damaged child and adult, to caring for and teaching cerebral palsied patients in special clinics and classes.

RESEARCH APPROACHES AND ADVANCES

Because cerebral palsy is observed first in childhood and appears usually to be the serious aftermath of processes occurring before or at the time of birth, research investigators are bent on learning when and how damage to the brain or nervous system occurs in the crucial perinatal period.

Collaborative perinatal project

Injury to the unborn child hidden in the mother's uterus is not evident before birth and, in fact, may not be recognized for a time afterward. Retrospective efforts to determine the actual cause or causes are usually limited. The Institute's "Collaborative Project on Cerebral Palsy, Mental Retardation, and other Neurological and Sensory Disorders of Infancy and Childhood" (referred to as the Collaborative Perinatal Project) is making it possible to obtain accurate information on the nature of injurious prenatal processes. It is also supplying essential

data on events during labor and delivery that may have a bearing on neurological and sensory defects and disorders in the offspring.

Within this study, being conducted in 14 major obstetrical centers, accurate and detailed pregnancy and obstetrical histories have now been recorded on over 60,000 women. Their babies will be followed up to the age of 8 years, in a series of special examinations designed to detect any neurological defect which may have resulted from unfavorable events of pregnancy. In this way, the events of pregnancy can be related to any unfavorable effects they may have had on the unborn child.

Project investigators are now engaged in an intensive evaluation of the data collected on the Study mothers and their babies born during the first 7 years of the project. The material collected to date—one some 4 million punch cards—contains records of infections and illnesses each mother experienced during pregnancy, the drugs she took, accidents she may have suffered, circumstances surrounding the birth of each baby, and many other health factors that each child has experienced since birth.

Several hundred children born to mothers during the first year of the Project are now 7 years old and about to undergo their final examination, completing the first Project study sample. Final analysis of all study data will not begin until 1974, when the information-collection phase of the Project is completed.

Although information analysis is preliminary, some statistically significant findings have already emerged. These include a marked increase in neurological abnormalities in premature children; the apparent relationship of general anesthesia given the mother during cesarean delivery to poor response of the baby at birth; and a wider understanding of the effects of certain drugs administered during pregnancy.

The true cause-and-effect relationships between factors harmful to the developing brain and resulting brain damage need to be correlated from the many facts that the Perinatal Project is amassing. These relationships are not easily established since many variables, such as infections, drugs, environment, heredity, and others, are involved in the prenatal, natal, and postnatal development of the nervous system.

This year, from the abundance of information that is being gathered by the Project, a number of additional findings have been uncovered; glomerulonephritis, a kidney inflammation in the mother, has been associated with low birth weight; diabetes mellitus with prematurity; maternal convulsions during pregnancy with a three-fold increase in mortality and morbidity of the infant; and vaginal bleeding as the most ominous obstetric sign relative to pregnancy outcome.

Other information revealed that mothers with severe heart disease did not have increased numbers of babies with serious neurological disorders; that therapy for incompetent cervix not only prolonged pregnancy to term but also resulted in a marked decrease in the otherwise significant number of unfavorable neurological consequences; that mothers' prior pregnancy records served as good indices for predicting future pregnancy results; and that fetal wastage was greatly increased in teenage and age groups above 35 years.

Excessive destruction of the red blood cells in the newborn may result in the hazardous accumulation of bilirubin, a bile pigment, in certain areas of the brain. This condition, identified by the yellow appearance of the infant's skin (infantile jaundice), can cause permanent damage. Criteria have been set to determine the need for exchange transfusion to avoid the danger of mental or motor retardation. One test is to measure the bilirubin level in the serum by chemical methods. A Project study of bilirubin levels and subsequent neurological deficits has shown that neurological damage occurs at levels lower than now considered "safe." This finding may require a revision of present criteria for exchange transfusion.

Results of data analysis showed a close correlation between birth weight and the "Apgar" score—a special test in the first minute after birth of the newborn's heart beat, muscle tone, color, and respiratory response. It was also shown that prolonged labor in itself was not deleterious unless associated with complications such as uterine dysfunction or difficult delivery.

Scientists are increasingly hopeful that the continuing detailed analysis of the massive data accumulated in the Project will make it possible to take steps toward preventing disease and injury in the perinatal period, thus averting permanent brain damage.

Laboratory of perinatal physiology

A major source of continuing experimental studies of brain damage in the newborn is the Institute's Perinatal Research Laboratory in Puerto Rico, where

primate studies are increasing knowledge of the causes of cerebral palsy and neurological and sensory disabilities in children. Comprising caged and free-ranging colonies of over 1,000 monkeys, this unusual study population is helping investigators to confirm leads or evidences of association between perinatal events and unfavorable pregnancy outcome obtained in studies of humans.

Studies of pregnancies in primates and their offspring include the experimental production of symptoms of cerebral palsy and other clinical syndromes, and the evaluation of methods to prevent and treat these conditions. In some ways, the Puerto Rican investigations parallel studies conducted by the Collaborative Perinatal Research Project.

Investigations continue on the specific role of asphyxia in brain damage. At the same time, other problems being explored include reductions in placental blood flow, umbilical cord clamping at particular times of pregnancy, and experimental placental insufficiency. Studies also are being conducted with rhesus monkeys on experimental production of bilirubin damage.

In addition, efforts have been started to produce placental abruption—a well-known complication in humans associated with a significant mortality rate and a high prematurity rate, with its known increase in central nervous system damage in survivors.

Among this year's research studies and findings in Puerto Rico that could have important implications in preventing cerebral palsy are:

Investigation of the role of placental insufficiency in producing neurological defects has been approached in several ways. One project concerns the anesthetic, nembutal, in conferring protection to experimentally asphyxiated animals. This study revealed a remarkable difference between infant monkeys delivered by cesarean section under local anesthesia versus those delivered by cesarean section under deep nembutal anesthesia. Those delivered under local anesthesia appeared more vulnerable to the onslaught of asphyxia and showed greater incidence of neuropathological change with a given degree of asphxiation. This important finding is being further studied.

In another project, experimental placental insufficiency resulted in an increase in the number of motor deficits in infant monkeys.

A third project linked umbilical cord compression with brain degeneration resulting in the formation within the brain of a fluid-filled sac (cyst). The degree of degeneration was well correlated with the duration of compression.

Placental abruption is known to have drastic consequences, ranging from death to the fetus to severe fetal brain damage. Until recently, little experimental work has been done on this problem. Studies of placental abruption initiated in the laboratory this past year are yielding a better understanding of pathological changes of the placenta.

The delicate and still highly preliminary technique of intrauterine transfusion of the fetus threatened by Rh incompatibility also occupied research attention in Institute laboratories. Previously, scientists in New Zealand devised a technique of intra-uterine injection of red cells, to replace the unborn baby's own Rh-positive cells, which were being destroyed by the anti-Rh antibodies in the mother's circulation. These antibodies cross into the placental circulation and dissolve the red blood cells of the fetus, a process called erythroblastosis fetalis.

Scientists in the Laboratory of Perinatal Physiology are attempting to determine, in animal studies, what percentage of transfused red blood cells actually reach fetal circulation following intra-uterine transfusion.

However tentative, present studies of fetal surgery may open up a chance to treat some of the blood-incompatibility problems at an early stage and prevent damage.

Other research projects

Research into the causes, brain changes, and symptoms of cerebral palsy and related organic brain syndromes is conducted by the Institute in its laboratories and clinics, both in Bethesda and elsewhere.

Detailed histological and histochemical examinations are being made of selected brains from deceased cerebral-palsied patients to establish more exact correlations with clinical observations. This approach is expected to provide clues on possible etiology and to help in outlining management and prognosis.

Brain pathology is also receiving attention in a project involving physically produced brain damage.

Another project at Bethesda is concerned with a clinical, biochemical, genetic study of CP, to provide further evidence of the natural history of the disease.

The tools and disciplines of all the neurological sciences are being incorporated in intramural efforts to ferret out more details about the cause, diagnosis, and pathophysiology of cerebral palsy.

TREATMENT

Research has contributed to forestalling measures against some causes of cerebral palsy. These include blood-compatibility tests in the prenatal period, and exchange transfusion of the baby at birth, where necessary to counteract the Rh factor and other blood type incompatibility; emphasis on maintaining good maternal health during pregnancy; preventive measures—where these are now possible—against prematurity and maximum protection of the prematurely newborn against disease or infection; alertness to the dangerous consequences to the fetus of rubella and other infections, and a stepped-up effort to develop a safe and effective vaccine against German measles.

Meanwhile, for the hundreds of thousands of children and adults who have cerebral palsy, various forms of therapy, depending on their individual type of the disorder, can help lessen handicaps.

A combination of therapeutic measures is often prescribed, including physical and occupational therapy, drugs in some cases to reduce muscle spasms, orthopedic surgery, special braces, and other programs involving speech and hearing therapists and other specialists in physical medicine and rehabilitation. All such programs need to be geared to developing the individual's total capacities and remaining motor skills to the fullest extent possible.

The Institute is deeply interested in the research aspects of rehabilitative therapy for brain-damaged children and adults and is participating in plans for a broad study to evaluate current therapies. At the same time it is supporting individual research projects related to treatment. For example, one project relates to the problems of the hip joint, where information is essential in the orthopedic study of the effects of cerebral palsy. Other projects relate to perceptual performance and learning abilities in children with CP, some of whom also have other forms of brain damage associated with learning problems.

Institute-supported neurosurgical teams are contributing to a more hopeful outlook for children with severely incapacitating movement disorders. These surgeons, employing stereotactic methods, are creating carefully placed lesions in certain areas of the brain.

One group of investigators has noted encouraging results of their operations on a small number of selected children, in whom all other methods of alleviating their intense symptoms (hypertonicity) had failed. Most of these children had cerebral palsy. Following surgery in the cerebellar region of the brain, the children showed a marked decrease in movement disorders, diminution of stiffness, relief of intense pain caused by muscle spasms, and in general appeared easier to care for and capable of deriving enjoyment from life. One child, who had been severely incapacitated, was able to walk and to be graduated from high school. The clinical results of this significant study were the outgrowth of years of experimental efforts to understand the interrelations of the various parts of the nervous system, particularly with respect to the motor centers which regulate movement.

Another grant-supported neurosurgical team utilized electrical stimulation to create therapeutic lesions in cerebral palsy patients. They implanted electrodes in a number of subcortical structures (striatum, thalamus, and mesencephalon) of the brain and correlated the effects of chronic stimulation in specific areas with the clinical picture. This information was then used to select the site or sites of the surgical lesion. Appreciable improvement was reported in at least one-third of the cases; the extent of improvement depended upon the area of the brain where the lesion was localized.

RESEARCH OUTLOOK

Recovery from the effects of brain damage remains one of the deepest medical challenges. Nonetheless, scientists are striving to find ways to repair injury sustained to the central nervous system and thereby provide a possible cure for cerebral palsy and other serious disorders. No one can predict when this extraordinarily complex task will be achieved. But the continuing research momentum should open the door to this possibility.

Future prevention of the causes of cerebral palsy remains as a prime target. Preventive steps for causes already discovered must be applied with vigor. The

search for causes still unknown must continue unabated. Pursuit of promising leads by scientific investigators throughout the country should reap even more exciting discoveries in the future.

SPECIAL REPORT: NEUROMUSCULAR DISEASES

More than 200,000 people in the United States are believed to have various neuromuscular disorders. Because of the slow development of certain types and the hereditary nature of many in which the carriers are unaffected, the number involved is actually considerably greater than the figure indicates. Most common neuromuscular diseases are the muscular dystrophies (MD), myasthenia gravis (MG), and the inflammatory nueromyopathies. The muscular dystrophies are particularly catastrophic to the patient and his family because the disease usually begins during childhood and progresses relentlessly. Some of the neuromuscular disorders do not shorten life expectancy but lead to disability.

The various neuromuscular disorders have one feature in common—moderate or severe weakness or paralysis of muscle. Only recently has clinical and laboratory experience reached the point where accurate differentiation of the many varieties is possible. In addition to clinical examination of the patient, this differentation requires exploitation of several newer techniques: electron microscopy—examination of the fine structure of muscle tissue; electromyography—measurement of electrical responses of muscle; tissue culture—growing muscle cells on artificial media to understand growth processes in normal and dystrophic muscle; muscle biopsy and histochemistry—microscopic and chemical study of muscle tissue—and general chemistry—study of blood and tissue chemicals and enzymes to detect generalized body chemistry alterations. Pursuit of these many approaches constitutes the Institute's main attack upon the neuromuscular diseases in an effort to define accurately the fundamental defect underlying each entity.

MUSCULAR DYSTROPHY (MD)

The muscular dystrophies are genetically determined disorders of muscle characterized by progressive wasting and weakness. Progressive MD (Duchenne form) occurs most often in males, beginning in childhood with limb weakness and overdevelopment of the lower legs. Facioscapulohumeral MD primarily affects face and shoulder girdle muscles, begins later, and develops less rapidly. In Myotonic dystrophy, wasting appears during adolescence and is associated with stiffness and involuntary contraction of muscle. Although no treatment for MD has yet proved effective, certain drugs which influence protein metabolism are being considered for evaluation. Meanwhile, with careful clinical management, some MD patients can increase their productive lives considerably.

There are three major research approaches to the muscular dystrophies. The first is an extensive study of the mechanical and microscopic structure of the muscle itself. This includes studies into the enormous complexity of muscle tissue in both the normal and abnormal state. There are a variety of chemical substances present in the muscles and certain stains localize their distribution. These stains are especially important to demonstrating existing abnormalities of their chemical structure. This microscopic recognition of structural abnormalities within muscle cells has led to the identification of three new forms of muscular dystrophies: central core disease, nemaline myopathy, and late-onset rod myopathy. Studies have also provided a better understanding of the chemical constituents of normal and dystrophic muscle.

Another area receiving special attention is the conversion of chemical energy into the main function of the muscle, the mechanical work. The place where enzyme deficiency might show up is in its relation to energy production. This failure may not be due to an abnormality in structure but in the production of energy. Eight or nine different forms of phosphokinase deficiencies have currently been identified. Also, four disorders associated with specific enzyme deficiencies have been discovered biochemically: deficiencies of phosphorylase, acid maltase, branching enzyme, and debranching enzyme. Phosphokinase deficiency affects one of the pathways for energy production in muscle. The discovery of the specific defect has led to rational methods of treatment. A study program is now being expanded in an attempt to establish whether there is a primary molecular disturbance distinct from the secondary changes that result from muscle breakdown or whether there is an environmental agent or agents functioning in addition to the primary molecular disturbance.

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There is also a major study program focused on the search for abnormalities of chemicals circulating through the body. It is possible that the muscle-membrane may be deficient allowing the essential material to leak in and out. Institute grantees and other researchers have now developed diagnostic tests that rely on abnormalities of circulating substances for detecting carriers of progressive muscular dystrophy. With this technique scientists can identify 65 percent of suspected genetic carriers of progressive (Duchenne) dystrophy by measuring the amount of an enzyme, creatine phosphokinase (CPK), in the blood serum. This is providing a method for sound genetic counselling to families where the disease is suspected. A program projected for the coming year is attempting further refinement of the methods. Also certain types of exercise that produce a significant increase in the CPK level, may aid in identifying borderline carriers.

Among accomplishments this year was the demonstration of two important aspects of myotonic dystrophy: (1) a specific atrophy of the "Type I" muscle fibers; and (2) an abnormal increase in the utilization of gamma globulin. A muscle disturbance has been discovered in two protein deficiency diseases—ataxia telangiectasia and acanthocytosis.

MYASTHENIA GRAVIS (MG)

In myasthenia gravis there is severe muscle weakness without wasting. Often the patient's strength is within normal range, but he develops extreme fatigue after little muscle exertion. The disorder may begin at any age, but most commonly strikes young adults. Its course is unpredictable, varying in intensity from crisis to remission. In MG, the nerve impulse is not transmitted from nerve endings in muscle, apparently because the chemical transmitter mechanisms fail. The weakness in MG patients can be ameliorated and often a life can be saved by giving them drugs which alter the chemistry of the neuromuscular transmission process.

For many years, it has been known that neuromuscular transmission depends upon the liberation at the nerve ending of a muscle excitatory substance called acetylcholine (ACH). In myasthenia gravis, this substance is either inadequate or ineffective. Drugs have been developed which enhance the activity of ACH, and thus ameliorate the symptoms. In many patients, such drugs produce marked symptomatic relief.

Myasthenia gravis is frequently, but not always, associated with tumor of the thymus gland (a gland in the chest). Removal of this gland, whether tumorous or not, appears to relieve the symptoms in some cases, but its ultimate effectiveness has been hard to evaluate due to the unpredictable course of the disease. The Institute has supported an extensive review of experiences with this surgical treatment. Improvement or complete recovery was found to occur in 89 percent of the female myasthenia gravis (MG) patients under 40 years of age when the thymus was surgically removed. These facts were obtained by evaluating 1,355 MG patients. Early surgery also eliminates the danger of malignant tumors (thymomas) of the thymus.

Recent discoveries indicate that the thymus gland plays a role in immunity. Interest in this fact is heightened by the discovery that in many patients with myasthenia gravis an antibody exists in the circulating blood with an affinity for muscle tissue. It has been postulated that in the patient with myasthenia gravis a distortion of the body's immune reaction causes the production of an antibody interfering with normal muscle chemistry.

Increasing emphasis has been placed on evaluating patients undergoing thymus surgery for the relationship between the level of antimuscle antibodies and serum complement (C′), with the change in clinical condition. Also further investigation is focused on the manner in which circulating antimuscle antibodies may disrupt physiological mechanisms in the post junctional membrane (pjm) of the neuromuscular junction. The importance of the pjm has recently gained additional emphasis by studies into the blocking effect of the anesthetic, halothane, recently favored with patients suffering neuromuscular disorders. Desensitization of the pjm was found to be the major factor in its effectiveness.

Some further support for the role of autoimmunity in myasthenia gravis is the action of ACTH, a drug known to suppress immune responses and inflammation. Its usefulness in myasthenia gravis has been a source of great controversy. An Institute-sponsored study carried out in 1964 indicated that small doses of the drug in mild cases were ineffective. This year, further studies reveal that larger doses may provide at least a transitory benefit in carefully selected severe cases.

OTHER NEUROMUSCULAR DISEASES

Major disability or muscular weakness also results from the periodic paralyses, dermatomyositis, and cancer-associated neuromuscular diseases.

The periodic paralyses are characterized by transient episodes of severe muscle weakness, and are associated with abnormalities in the amount of potassium circulating in the blood. These inherited disorders are now accurately classified and remarkedly well controlled. In cases where the cause is associated with thyrotoxicosis, a cure is usually possible by removal of the thyroid gland.

Dermatomyositis includes chronic inflammatory diseases of muscle which lead to painful stiffening and eventual incapacity. While an infectious origin is suspected, specific agents have not been found for the majority of forms. Dermatomyositis may begin at any age and is usually progressive if untreated. Recent discoveries are providing a cure for some of the cases.

Certain forms of cancer produce changes in body chemistry and cause disorders of muscle which closely resemble the dystrophies and dermatomyositis. Often the cancerous origin of the muscle disease does not appear in a recognized form.

Important developments are being made in the understanding and control of these disorders. Current studies on dermatomyositis are attempting to determine the actual sensitivity and to modify the effects. Also findings concerning remote cancer as a cause of lateonset neuromyopathy and its sex-related incidence are aiding in providing important diagnostic leads for physicians. The nature of the process by which the cancer induces myopathy continues to be the subject of intensive Institute-supported research. And because genetics is fast becoming an important discipline in the study and prevention of many of these other inherited neuromuscular disorders, efforts are being concentrated on developing additional genetic screening tests similar to the CPK assay for detecting carriers of progressive muscular dystrophies.

PROGRAM DEVELOPMENTS AND FUTURE PLANS

The Institute's research program relating to neuromuscular disorders includes support of individual investigations and the training of clinical investigators in basic neurophysiology and neurochemistry techniques. With the availability of more personnel trained in basic and clinical neurological research, an expansion of the Institute's programs in this area will be possible.

Because the understanding of complex diseases requires a multi-disciplinary approach, the study of neuromuscular disorders has been an important segment of the Institute's research program at its Bethesda laboratories. Upon completion of the new NINDB-NIMH research building, increased space and facilities will be available for neuromuscular disease studies.

Plans for broadening the Institute's attack on neuromuscular disease include support of clinical research centers specializing in the neuromuscular diseases, a drug evaluation program, development of effective screening methods to detect persons with inherited neuromuscular and other neurologicsal disorders, and support of scientific communication through publications and conferences.

Clinical research centers

Two university-based clinical research centers concentrating on the study of neuromuscular diseases have been established with Institute support at the University of Pennsylvania and at Columbia University. The Institute supports a large research and training center on the physiology of muscle at Harvard and underwrites a similar basic science unit at Columbia, concentrating on chemical aspects of neuromuscular transmission. One additional research center in the neuromuscular diseases will be supported next year. In the research centers, scientists representing many disciplines have been brought together to focus their combined skills on basic and clinical research in the varied aspects of the neuromuscular system in health and disease.

To further strengthen its program, the Institute has developed under the P.L. 480 program, a collaborative project at the Academy of Medicine, Warsaw, Poland. The clinic in Warsaw has been designated as a center to which neuromuscular disease patients from the entire country are referred. Scientists there are developing competence in electron microscopy, histochemistry, and general chemistry methods to parallel and complement studies in progress in Bethesda. Exchange of scientists furthers this effective collaboration. The Institute plans to support similar collaborative studies at other medical centers. For example, scientists at the center at Columbia and in Yugoslavia have a common interest

and capability for the study of the mechanism and chemistry of neuromuscular transmission.

Drug evaluation

Effective drug therapy for the neuromuscular diseases remains a major need. The Institute has encouraged improved methods of drug evaluation through its clinical neurological centers, and some success with new chemotherapeutic agents has been achieved in this program. For example, Institute physicians have helped to clarify the criteria and methods of use of corticosteroids in treating collagen-vascular diseases—neuromyopathies affecting nerve, muscel, blood vessels, and connective tissue.

In the evaluation of therapy of myasthenia gravis, the Institute in collaboration with the Myasthenia Gravis Foundation conducted a study of ACTH in ocular myasthenia and a grantee reviewed thymectomy for treatment of MG. The Institute is now supporting development of methods for evaluating muscular dystrophy therapy.

Publications and conferences

Institute scientists have prepared a monograph on "Current Concepts of the Myopathies," and recently have written chapters on the tissue chemistry of neuromuscular disease in six monographs.

Two major international scientific meetings, in which the Institute has had an important part, have been the international symposium on "Exploratory Concepts in Muscular Dystrophy and Related Disorders" organized by the Muscular Dystrophy Associations of America, and the conference on "Experimental Myopathies and Their Relationship to Human Muscle Disease" called by the New York Academy of Sciences. Important new developments were reported and major goals and needs were identified, the most urgent appearing to lie in a closer link between the hospital and the theoretical laboratory in making material and findings more readily available. Other specialized conferences, designed to stimulate scientific communication among experts in the neuromuscular field, also have included the following topics: "Biophysics of Excitable Membranes," "Mutant Mice with Neurological Diseases," and "Myasthenia Gravis."

SPECIAL REPORT: MULTIPLE SCLEROSIS

THE PROBLEM

It is estimated that approximately 500,000 Americans are afflicted with multiple sclerosis (MS) and such closely related disorders as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy, and allergic encephalitis.

Multiple sclerosis, the most common of this group of disorders, is a major disease of the central nervous system, in which myelin, the fatty, protective tissue sheathing the nerve fibers, disappears in scattered patches. It afflicts more than a quarter of a million Americans, primarily between the ages of 20 and 40 years.

The disorder, chronically progressive in the majority of affected persons, proceeds in a series of unpredictable attacks. In earlier stages, attacks are often followed by periods of remission. With successive episodes, resulting lesions in the brain and spinal cord become more dense and destructive, causing more severe disability.

Geographically, the incidence increases as the temperature of the climate declines. In the northern States, its incidence is 40 to 50 per 100,000 population, while in the South the number of cases drops to as low as 10 to 15 per 100,000 population.

The causes of multiple sclerosis and mechanisms by which the disease is produced are both unknown. Despite the increase in basic research information, no dependable treatment to ameliorate or specific therapy to counteract the disease has become available.

Amyotrophic lateral sclerosis, another member of this family of disorders, is of particular research interest because of its geographic distribution. Although comparatively rare, this disease is prevalent on the island of Guam and certain of the nearby Marianas, where a form of ALS is over 100 times more common considering the size of the population than in the continental United States. This unique situation provides an opportunity to search for specific causative agents that may be responsible for producing the disease.

RESEARCH APPROACHES

The studies in MS have been directed mainly to understanding the biochemistry of the disease, its geographic distribution, and its possible relation to allergic encephalitis and viruses.

Of the four major research approaches to MS, epidemiology of the disease was probably the first to be extensively investigated. This is the science dealing with the relationships of the various factors which determine the frequencies and distributions of disease in a population.

Multiple sclerosis is confined almost entirely to regions having a temperate or cold climate. It is many times more prevalent in Canada or northern United States than in the southern areas of this country, and almost unknown in the tropics. Institute-supported studies in the U.S.A. and around the world have amply confirmed this important clue. Even more important, studies of afflicted soldiers have demonstrated that it is the climate within which one has spent one's childhood, and not where one is living when the disease manifests itself, that is important.

In Israel, a study of MS patients has not only confirmed the higher prevalence of this disorder in immigrants from temperate latitudes but has also indicated that the onset of the disorder may be as long as 10 or 15 years after leaving the temperate climate for the subtropical area. Data to support this conclusion are found in the incidence rates which are much higher in Europeans immigrating between the ages of 15 and 29 than in the youngest age group, those less than 15 years old. These data suggest that multiple sclerosis is acquired, at least in many cases, before age 15 years. However, it is unlikely that the disease is acquired at birth or in early infancy since migration from Europe to Israel before age 15 years appeared to have had a protective effect.

These epidemiological evidences are receiving further study to determine what other social or environmental factors are operative. Preliminary data suggest that the more favored socio-economic groups may be particularly susceptible. In a study of 1,000 U.S. veterans which the Institute is conducting with the Veterans Administration and the National Research Council, it has been found that a larger number of veterans from the cities have multiple sclerosis than those from the rural areas. It was also found that men and women with higher education and earning power are most susceptible to the disease.

The study of viruses is a second approach. One possible explanation for the long latency and the recurrent nature of the disease is a slow or latent virus infection. Viruses have been under suspicion and have been investigated as a possible cause for this disease for many years. Viruses could cause the disease by damaging the nervous system and by liberating a fraction of the very complex protein and lipid material that make up the nervous tissue. The demonstration that viruses may lie dormant in the nervous system for long periods of time in other diseases, such as herpes simplex and the disease of sheep called scrapie, lends support to this possibility.

This year this thesis has received additional support through the discovery of an agent transmitted to chimpanzees from patients suffering from a mysterious degenerative disease called kuru. The condition bears some resemblances to multiple sclerosis, and suggests that MS may have a similar basis. This research was conducted at a special virus laboratory established by the Institute at Patuxent, Maryland, in cooperation with the Fish and Wildlife Service, Department of the Interior. Here material from patients suffering not only from kuru but from multiple sclerosis, amyotrophic lateral sclerosis, and related diseases is being injected into primates and other animals in the search for a transmissible agent. For the development of this study, a considerable number of animals will have to be retained in absolute isolation for from 5 to 10 years.

In a closely related study partially supported by the National Multiple Sclerosis Society, serum from patients with multiple sclerosis is being tested for antibodies against a number of the common viral diseases. It is postulated that these common diseases may occasionally produce MS as an atypical reaction to the virus. Possibly such a virus reacts with brain tissue to initiate an autoimmune reaction as described below.

Another major research effort is being directed toward understanding the biochemistry of the disease. A characteristic feature of MS is liquefaction of the fatty sheath surrounding the nerves. One focus of the Institute's program has been on the chemical processes involved in the formation and destruction of this fatty sheath, called myelin. It is possible that a nutritional or toxic factor might be responsible for this tissue breakdown.

Experimental demyelination is a fourth approach to the study of MS. Since liquefaction of myelin is a characteristic feature of MS, the experimental production in animals of such a reaction is an important research tool. One means whereby this can be accomplished is through experimental allergic encephalitis (EAE). Normally, the body's protective immunity is directed only toward the destruction of foreign substances or germs introduced into it from outside. Under certain abnormal circumstances, the body may direct its immune defenses against its own tissues. Thus, if specially prepared brain extracts are injected into an animal, the animal's immune defenses are mobilized and attack the animal's own brain tissues. Demyelinization bearing many resemblances to MS may result. The belief that such a mechanism may be operative in MS has been strengthened by the observation that, when serum from patients with MS is applied to nerve cells in tissue culture, liquefaction of the myelin sheath occurs. The study of nerve growth in tissue culture, and the reactions of this tissue to antiserum, toxic agents, and drugs is therefore important in the study of MS.

Although anti-myelin antibodies have thus been demonstrated in the blood serum, there is evidence to suggest that the circulating blood cells (lymphocytes) may play an essential role in antibody production and in the autoimmune process, because lymphocytes produce most antibodies. Over-reactivity of the lymphocytes in patients with multiple sclerosis was recently suggested from studies in which lymphocytes from patients and controls have been caused to interact with spinal fluid. Changes in th lymphocytes called transformations occurred more commonly in the MS patients. This test may prove to be a useful diagnostic tool.

Additional studies are now seeking to determine the specific brain substance (probably protein) to which the body becomes sensitized, the tissues within the body through which the antibodies are produced, the structures in the brain which are specifically attacked by the autoimmune process, and most important, the means whereby such an autoimmune process can be blocked.

An agent known to reduce the body's immune responses is ACTH. It has been suggested that this drug could be useful in reducing the severity of attacks of MS. To test this possibility, the Institute has organized a cooperative therapeutic trial to determine whether ACTH is effective in treating the relapses of MS.

It is now becoming evident that MS is a well-defined disease entity. The consequence of its destructive process in the brain is specific. Some characteristics of the causative agent or factor, and the details of the course of the disease have been outlined. The Institute now has a well-rounded program, involving its intramural laboratories at Bethesda, and many independent scientists in laboratories across the country. Within these laboratories studies focused on the key problems relating to this mysterious disease are in full progress.

SPECIAL REPORT: CEREBROVASCULAR DISEASE

THE PROBLEM

Today, cerebrovascular disease (cause of strokes) ranks third in causes of death in the United States. Reports indicate a 21 percent mortality following an initial attack of cerebral thrombosis, one of the major types of stroke. Moreover, of the 79 percent who survive the first attack, one-half die within the next four years, the remainder often condemned to a life of either permanent paralysis or other neurological catastrophe.

While cerebrovascular disease occurs in children and young adults, most deaths from cerebrovascular disease occur in older persons. Deaths from subarachnoid hemorrhage, for example, are more common between the ages of 40 and 60, whereas cerebral hemorrhage and thrombosis show increasing incidence with age. Of about 2,000,000 victims of cerebrovascular disease alive today, about one-third are wage earners made unemployable by the residuals of a stroke.

With the number of person over 65 on the increase (18 million now and 20 million by 1970), the problem can be expected to remain a serious one even though modern medicine may be able to provide more successful treatment than in the past.

The term "stroke" refers to loss of brain function resulting from interference with the blood supply to the brain. Some strokes are minor episodes, while others cause permanent disability. Usually they are brought on by one of three events: thrombosis—a clot within a blood vessel of either the brain or the neck; cerebral embolism—the blocking of a blood vessel in the brain by a piece of clot carried through the circulation from some other part of the body; or cerebral hem-

orrhage—the rupture of a cerebral blood vessel with bleeding into the brain tissue.

The major underlying cause of cerebrovascular disease is atherosclerosis—a disorder in which deposits of fatty materials form within the inner lining of an artery wall and decrease the size of the arterial channel. The decreased size of the blood vessels limits the flow of blood and increases the danger of complete blockage at some point. People with hypertension (high blood pressure) also show a considerable increase in the severity and frequency of vascular diseases of the brain, especially cerebral hemorrhage. Among other causes are aneurysms—usually congenital weaknesses in artery walls that develop into sac-like swelling—and abnormalities in the blood clotting mechanism which facilitate clot formation.

Whatever the specific mechanism involved, interference with the blood supply of the brain inevitably leads to the death of brain cells and impairment of function. Temporary or permanent paralysis of movement, though, speech, or sensation is the result.

A concerted attack on the problem of cerebrovascular disease is being made by the National Institute of Neurological Diseases and Blindness (NINDB) and the National Heart Institute (NHI) through the effort of a joint subcommittee of the advisory councils of the two Institutes, and by groups of scientific consultants

THE PROGRAM

The NINDB has recognized stroke as a major health problem, and has supported research through project grants for many years. Beginning in 1961, with the overall broadening of research support mechanisms at NIH, the Institute understook support of multidisciplinary research centers for the study of this disease, and there are now 15 such centers (a 16th is supported by the National Heart Institute) located in major population centers of the country. Each center is concentrating on a major approach to the disease problem, such as epidemiology, natural history, the dynamics of cerebral blood flow, the biochemistry of blood constituents, the effect of anticoagulant drugs, and cerebral cellular metabolism. In addition, each center is giving major emphasis to clinical research on problems of improved diagnosis and treatment. The work in all the centers is coordinated by the Joint Council Subcommitte through symposia at which scientists report findings and exchange ideas. Together, these men spearhead a major attack on the fundamental problems which must be solved before strokes can be prevented and treated more effectively.

In addition to the research grants program, a contract has just been negotiated for a national epidemiological study of stroke. Six to nine communities will serve as the basis for data which will be gathered and analyzed for comparisons of customs and practices in certification of deaths. These data will be correlated with hospital records and with physician and household interviews to determine their adequacy. If necessary, other methods of obtaining epidemiological information will be explored. For the first time accurate information will become available about the incidence and mortality of cerebrovascular disease and the validity of the reported differences in different parts of the country.

The number of research and clinical workers in the field of stroke is still far from adequate, and the Institute last year began to expand its cerebrovascular training efforts, organizing specific training programs for each of the different professional groups concerned. Since the founding of the Institute, training in all of the academic neurological disciplines has been supported, but sponsorship has now been extended to a number of programs specifically for training in cerebrovascular research, including several types of support which provide short-term training to medical practitioners who wish to keep abreast of the latest developments in diagnosis, prevention, and treatment, longer training for specialists in internal medicine, surgery, radiology, and physical medicine, and long-term training for future teachers and investigators.

The cerebrovascular program of the NINDB, both in research and training, is closely coordinated with the programs of the National Heart Institute and the NIH Division of Regional Medical Programs, with a view toward bringing the fruits of the scientific effort into clinical practice in all localities as rapidly as possible.

Cooperative studies

Much can be learned about cerebrovascular disease only through cooperative studies, because of the vastly enlarged statistical base made possible through the combined efforts of a number of institutions. The Institute has been supporting

a Cooperative Study of Intracranial Aneurysms and Acute Subarachnoid Hemorrhage, among 24 university-based centers here and abroad, since 1958. Personnel at a central registry at the University of Iowa have now analyzed the accumulated data on 6,368 cases and have published a wealth of carefully derived statistics of value to physicians in deciding upon courses of treatment. The study has produced data on the most common causes of subarachnoid hemorrhage, susceptibility of various age groups, sex distribution, most common sites of aneurysms, sites related to age and sex, percentages of patients who had warning signs, the relation of environmental events to hemorrhage, and the value of angiography in detecting multiple aneurysms. Also produced were new analyses of the mortality of non-surgically treated cases, the risks of death and of rebleeding at various time intervals after hemorrhage, the statistically critical size of aneurysms, and the influence of age, sex, aneurysm site, and general patient condition on survival.

Among the many highlights of the study was the statistical verification of intracranial aneurysm as the most common cause of subarachnoid hemorrhage (51 percent). Next most common is hypertensive arteriosclerotic cerebral vascular disease (15 percent). Other findings were that the peak frequency for hemorrhage due to aneurysm lies within the 50–54 age group, and that hemorrhage from aneurysm is more common in women by a ratio of 3 to 2, though men predominate below age 40. The study revealed that headache and dizziness occur before hemorrhage in at least 90 percent of the cases, but noted that these are so commonplace as to be of little diagnostic value. In one-third of the cases, hemorrhage occurred during sleep; in another third, during random activity. However, certain specified events showed a higher frequency of association than expected, including lifting and bending, and emotional stress. The scientists found that high-quality bilateral carotid angiography can be used to discover 92 percent of multiple aneurysm cases, but that the remaining 8 percent require vertebral angiography in addition.

With the discovery and utilization of effective anti-hypertensive drugs, there has been a corresponding decrease of the number dying of strokes. The Institute is now funding a new cooperative study of hypertensive patients showing signs of cerebrovascular disease at eight institutions, in order to learn the degree to which anti-hypertensive drugs decrease stroke incidence.

In the planning stage is another cooperative study which will be a joint effort of the NINDB, the Veterans Administration, universities, and the National Academy of Sciences. Using the very large study population whose records are available from the Veterans Administration, epidemiologists and neurologists will develop much more detailed and accurate data on incidence and possible factors affecting incidence.

Scientific conferences

The Institute has sponsored scientific meetings, both on the broad topic of cerebrovascular disease, and on specific aspects of the problem. The Fifth Princeton Conference on Cerebrovascular Disease was held in January 1966, and plans are being made for a sixth to be held in 1968. Conferences on specific cerebrovascular problems include one devoted to the neurology of aphasia, in November 1965, and one on the rehabilitation of stroke victims held in March 1966. A workshop for the scientific directors and staffs of the 16 cerebrovascular clinical research centers is planned for January 1967. The Joint Council Subcommittee will continue to meet three times a year serving as a focal point for cerebrovascular planning and giving general guidance to the program.

NEEDS

The great advances in knowledge, instrumentation, and techniques of medical science as a whole in the past two decades have led to a more optimistic attitude toward prevention and treatment of stroke. The substantially enlarged Federal program of research support in the field has heightened this optimism. Much remains to be done, however.

The epidemiology of stroke, which could identify the causes of the disorder, is still largely undeveloped. Rapid survey methods should be developed which can be used reliably in large-scale population studies by field investigators. More prospective studies of large population groups beginning at age 30 are needed to uncover factors contributing to stroke proneness.

The importance of blood-flow studies has repeatedly been emphasized, and is a central interest of several of the clinical research centers mentioned earlier. Scientists at one of the centers have developed highly accurate new electronic methods for recording rapid changes in cerebral blood flow and metabolism as a direct write-out on a graph.

However, the dynamics of circulation are only part of the problem; there needs to be adequate understanding of the mechanisms that promote and retard clotting. Blood clotting is a normal physiological defense mechanism when it occurs at a point of injury in a blood vessel; it becomes abnormal when it occurs within the closed vascular system of a previously normal person.

Significant advances have been made in the rehabilitation of stroke patients. However, many thousands of stroke patients lie helpless in nursing homes, slowly deteriorating toward states of organic dementia, who might be helped substantially through modern techniques. The encouragement of research in restitution of function is a major concern in Institute planning.

Continued autopsy studies can contribute much to the accuracy of our knowledge of the pathology of stroke. For example, a neuropathologist supported by the Institute has reported that 2,650 brain dissections made over a 7-year period show that intracranial thrombosis is more frequent, in relation to thrombosis of the carotid and vertebral arteries, than is currently believed.

Training for research in cerebrovascular disease is one of the field's most urgent needs. The Institute's training program has greatly strengthened the Nation's research manpower resources in the neurological field generally, having provided training support in the clinical and basic disciplines pertinent to the cerebrovascular field. With new forms of training support established last year, it is hoped that more of the scientists who have been trained in neurology, neuroradiology, neurosurgery, and other directly related disciplines will now be encouraged to undertake specialized study in cerebrovascular disease. Scientists from associated disciplines such as genetics, epidemiology, biostatistics, and biomedical engineering also need to be encouraged to focus their interest on stroke problems.

With a number of Americans moving into the primary target age for strokes, it becomes increasingly urgent that the Institute's broad but intensified research and training effort continue to move ahead with the vigor and speed demanded by the scope of the problem.

SPECIAL REPORT: DISORDERS OF HEARING, LANGUAGE, AND SPEECH

THE PROBLEM

Disorders of hearing and speech, and neurological disorders which hamper or prevent language development are major national problems. This is true not only because of the large number afflicted and the health problems involved but because of their associated educational and economic implications. Because these disorders are so interrelated, they are usually referred to as the communicative disorders. This general concept also includes problems of voice and reading disability.

It is impossible to make a specific statement about the prevalence of communicative disorders; available statistics are inadequate. However, what is known warrants thoughtful consideration.

Infants

The evidence from the Institute's Perinatal Research Project indicates that by one year of age, 12 to 15 percent of children are neurologically deviant to some degree. For various reasons, 10 percent of the Project's live births are premature; of those weighing under 1,500 grams, more than 50 percent will have profound problems, including those of hearing, language, and speech, alone or in combination.

Children

Among children, it is estimated that 12 out of every 10,000 in the population are totally deaf and that between 150 and 300 of every 10,000 suffer from severe hearing impairment. About 500 per 10,000 have some type of disorder of speech which affects articulation while 20 per 10,000 suffer from cleft palate, facial malformation, or other organic disorders affecting speech. Cerebral palsy afflicts 13 out of each 10,000 of this population; half of these have some hearing, language, or speech problem. Fifty out of every 10,000 children suffer retardation in speech development not caused by deafness. Voice problems are estimated at more than 60 per 10,000. Stuttering (not necessarily to be considered a speech disorder), affects 60 in every 10,000. In short, this means that 10 percent of the Nation's children suffer from some form of communicative disorder.

Specific dyslexia is a diagnostic term applied to a type of reading disability. The entity involves reversal of symbols, auditory confusion, and writing problems—including mirror-writing. The problem is far more serious among males, with a ratio of 14 boys to every girl afflicted. This kind of impairment may involve as many as 3 percent of school-age children.

Adults

In the adult population between 25 to 44 years, hearing impairment amounts to more than 400 per 10,000; severe speech disorders have not been reported in credible estimates (the validity of one estimate, 65 per 10,000 population, has been questioned).

In an older adult group, age 55 to 65 years, hearing impairment affects more than 800 per 10,000, while speech disorders appear to remain at the 400 per 10,000 rate.

By age 75 and over, hearing impairment amounts to more than 2,500 per 10,000. There are no adequate estimates of the prevalence among the older groups of speech and/or language disorders. However, it is well known that between 1,500 and 2,000 laryngectomies are performed each year for laryngeal cancer and that there are between 15,000 to 20,000 who have had this operation. Since the larynx is essential for normal speech, these persons are able to speak only through a complete retraining process.

Thus, despite the fact that firm counts for these various communicative disorders are not available, it is apparent that they constitute a major problem, and that a large proportion of the more serious of them are neurologically based.

Causal factors

The causes of deafness are numerous and varied. Many are congenital in origin. Included among these are some of genetic origin and some due to prenatal injury by toxins or infection. Maternal German measles, for example, has been proven to be a particularly important cause of congenital hearing impairment.

Deafness may also have its origin in the early neonatal period. Jaundice of the newborn often due to blood type incompatability of the mother and child (erythroblastosis) is a cause of hearing impairment and language deficit. Asphyxiation at birth is another similar cause. Bacterial infection in the neonatal period is common, especially in prematures, who may suffer permanent impairment as a result.

Many kinds of postnatal damage may affect the auditory system: head trauma, viral infections, pyogenic and influenzal meningitis, encephalitis, upper respiratory infections and secondary pyogenic infections (these account for almost 80 percent of hearing impairment within school-age groups) drug toxicity, and, occasionally in childhood, commonly in adulthood, otosclerosis. Without doubt, presbycusis or hearing impairment in the aging processes, is caused by a combination of atrophy and exposure in a noisy world.

Relative to language and speech problems, the picture is less definite. Many kinds of neurological or psychological disturbances or developmental anomalies may interfere with learning and remembering language meanings and with fluent speech output. Gross intellectual deficiency or maxillo-facial developmental anomalies are obvious causes, as is cerebral palsy in its various forms. It is clear, as well, that psychosocial deprivation is a major cause of deviation in language comprehension and delay in speech development.

Hearing disorders, genetic factors, and general intelligence are all causes of trouble in learning language and in speaking.

PROGRAM DIRECTION

The Institute supports an extensive research and training program relating to disorders of communication. This program includes many individual basic and clinical research projects at various medical centers; basic research at the Institute's laboratories in Bethesda; five multidisciplinary human communication research centers; a special emphasis on communication in the Institute's Collaborative Perinatal Project; and a newly created scientific information center on human communication.

Council subcommittee

To review the entire field and identify areas of need, an NINDB Council Subcommittee on Human Communication and Its Disorders was formed by action of the Institute's Council early in 1965. Specifically, it was asked to provide:

(1) a definition of the field of human communication and its disorders with emphasis on "the communication sciences"; (2) a determination of the prevalence of various disorders; and (3) an outline of unresolved problems and unmet needs. Clearly, this is an extensive undertaking. It is estimated that it will require 3 years; and that it will probably terminate with a national conference early in 1968.

Institute conference at Princeton

Last year the NANDB Council brought together at Princeton some of the world's outstanding authorities and researchers on the problems of "Brain Mechanisms Underlying Speech and Language." This conference offered a resume of the present state of knowledge, and indicated specific areas of research opportunity.

Research centers

Five multidisciplinary centers covering various aspects of human communication research are being supported by the Institute. An investigation of the fundamental processes of hearing is under way at Princeton University. A program at the Central Institute for the Deaf in St. Louis is focused on problems of auditory communication and its disorders. At the University of Chicago, a unit of research beds was opened earlier this year to hospitalize cases of poorly understood types of deafness and vertigo as well as patients with disorders of vision. The Kresge Hearing Research Institute at Ann Arbor, Michigan, has been concerned with the causes of deafness, and work of scientists at the University of Florida includes physics and physiology of voice production, the psychology of speech behavior in children, parent-child communication and first language acquisition, linguistics, and voice pathology.

In addition, the Institute's cerebrovascular center at Boston University is emphasizing research on aphasia.

Perinatal project

The Institute's Collaborative Perinatal Project, involving the study of more than 60,000 pregnancies and their outcome, is beginning to provide a fund of information about prenatal and perinatal factors causing communicative disorders.

In addition to an infant screening test, a "High Risk Register for the Better Identification of Children with Problems of Communication" has been developed, which covers antenatal factors, complications of labor, neonatal difficulty, factors in early childhood, and psycho-social factors. This register can be put to excellent use for purposes of screening for case detection, particularly in communities where direct screening and adequate special clinical facilities do not exist.

A third important aspect of the studies is an examination of infants at 36 months of age to evaluate their developmental status in terms of hearing, language, and speech.

Consideration is now being given to the inclusion of a corresponding examination when the children reach age 8.

Scientific information center

The rapid increase in research and in the volume of research publications in the area of human communication makes necessary an efficient means of reviewing, evaluating, and disseminating information of significance and use to the scientific community. This is being undertaken by a newly developed Institute-supported Information Center on Human Communication and Its Disorders at The Johns Hopkins University.

RESEARCH DIRECTION

Attention focused on the very young

Major research emphasis of the 1966 NINDB-supported program into hearing, language, and speech impairments has been focused on (1) the causes that have their origin in the perinatal period, infancy, and early childhood; and (2) special techniques for early diagnosis and treatment. Early recognition of any defect of the hearing or speech mechanism is crucial to the learning process and the social development of the future citizen. It is estimated that today 100 percent of the Nation's children suffer some form of communicative disorder.

Rubella tied to deafness and ear infection

Maternal rubella infection (German measles) was found to cause a considerable number of babies to be born deaf. In addition, this year's studies showed that

babies born of mothers who had rubella but were not born deaf were, however, particularly predisposed to secondary middle ear infection endangering them to hearing loss. Detailed records of the Collaborative Perinatal Project are providing data on the magnitude of the problem as well as material for extensive study into the way in which maternal rubella effects the hearing mechanism of the child.

In one of the institutions collaborating in the Perinatal Project, 1,353 women in the study were pregnant during the epidemic of 1964. Approximately 10 percent of these pregnancies involved prenatal rubella, confirmed by virological or serological tests. Of these, almost half of the babies were carriers of live virus after birth for varying periods of time.

Study of the infants born under these circumstances have provided new and important information on the effects of maternal rubella on hearing. In cases where this association is known, prompt recognition and treatment of ear infection can often be accomplished soon enough to prevent much of the progressive hearing loss which has previously been occurring in these infants.

Revised concept of bone conduction

Sound waves are conducted to the organ of hearing in two ways—one through the air to the eardrum and the other by passage through the bones of the skull.

A revised concept of bone conduction of sound waves to the inner ear, based on 5 years of experimental work, promises to enable physicians to interpret more clearly the variations in bone conduction measurements found in ear diseases. The main points of the theory involve the three kinds of waves elicited by sound and the three modes of bone conduction responses of the ear. These findings have been integrated with prior knowledge of bone conduction.

A Research Career Awardee of the Institute has noted that the response of the normal ear to sound integrates all three modes and the various modifying components according to their amplitude and phase relationships. He emphasized that when specific parts of the ear are missing or functionally eliminated the total bone conduction response is altered accordingly.

Temporal bone bank program

Bequeathed inner ear structures from persons with a long medical history of hearing problems are being studied through the Temporal Bone Bank Program. Within this program, studies of the organs of hearing and balance, hidden deep within the temporal bone, inaccessible for study during life, provide an important means of uncovering essential facts on hearing disorders in human beings. A detailed study of human temporal bones may well provide the key to correlating structural and pathological changes with functional disorders of the auditory and vestibular systems. There are now some 30 cooperating temporal bone banks and laboratories located in major cities across the country.

Recognition and classification of communicative disorders

There are several points of particular importance in the detection and management of those with communicative disorders. First is the need to employ a common, systematic nomenclature in describing communicative impairments. Second is the need for identifying the affected children and adults as soon as possible. Third is the need for standard tests and measurements, with clearly expressed criteria for success and failure.

The Institute's program is contributing materially to all three of these basic needs. Workshops on nomenclature are being held with national coverage in order to cover the so-called "consumer groups," hospitals, rehabilitation centers, and welfare services.

A major development has emerged from the study of infants in the Institute's perinatal Project. A simple "distraction test" of responses of babies to acoustic stimuli has been given to several thousand infants. Approximately 10 percent fail at both 4 and 12 months. Of these, 4 in 10 have treatable middle-ear impairment associated with recurrent upper respiratory infection; 3-to-4 in 10 have some aspect of neurological deficit or deviation; and 5-to-6 in 10 have some kind of mental deviation. This simple screening test may become a powerful public health tool in case detection.

A considerable variety of research grants in the Institute's general research program is devoted to the development of further tests and measurements. This is particularly pertinent to three important aspects: (1) the refinement of speech-hearing tests of intelligibility; (2) the development of "mixed-message" tests for the better definition of auditory disorders of central pathways; and

(3) the use of averaging computers in the study of electrophysiologic responses to sound, particularly with infants and young children; several projects are concerned with norms and validating procedures.

Drug evaluation

This year, there has been an intensification of studies of the harmful and beneficial effects on hearing of a broad range of chemical substances. Sodium fluoride is showing favorable laboratory results in treating one type of otosclerosis, a major cause of deafness. Minute amounts of sodium fluoride, a chemical commonly used to guard against dental cavities, has been demonstrated not only to have the ability to increase the deposit of calcium in bones, but also to retard the overgrowth of spongy tissue. This is providing a new approach to the control of otosclerosis of the cochlea, where a mass of spongy tissue can cause deafness by filling the lower area of the inner ear. Small amounts of sodium fluoride appear to be able to cause the system to reabsorb the tissue and restore hearing. (Cochlear otosclerosis is not to be confused with the tye of otosclerosis where the stapes—one of the three tiny bones of the middle ear—has become immobilized so that it cannot transmit sound. A highly successful technique for surgically freeing the stapes and restoring this type of hearing loss is already in use.)

Investigation into the way in which the mycins (especially streptomycin) and the members of the chloroquine family act on the hearing and balance mechanisms of the ear are providing important information to aid in keeping dosage levels within the safety zone. Further study into the effect on loss of equilibrium (vertigo) by viomycin, a drug holding a major position in treatment of respiratory tuberculosis, is providing guidelines to physicians.

Basic research

Computer techniques, applied to the analysis of electrophysiological responses, have been helpful in studying the auditory system recently. These electrodermal and electroencephalic responses are obtained by recording minute electrical currents of the skin and from the skull. The computer techniques made it possible to compile basic data on such responses by sex, age, and race; and also the repeatability of responses of both normal and abnormal subjects. These data greatly extend the usefulness of these methods in the study of abnormalities of the auditory system and are essential to their development into methods which eventually can be used in clinical practice.

Understanding of disease processes in the inner ear was further advanced during the past year by studies which clarified the source of the blood supply to the end organ of hearing; described the variational anatomy of certain portions of the inner ear; and increased the understanding of the fluid balance in the inner ear. Each of these basic studies have important implications for surgery of the inner ear.

Nerve deafness

The effective handling of certain types of deafness, it is hoped, may eventually develop from a new method of directly stimulating the hearing nerve reported by NINDB grantees. In one study, the auditory nerve of a 60-year-old man suffering bilateral sensory-neural deafness was subjected to direct electrical stimulation over an extended period of time. Six microelectrodes were permanently implanted directly in the auditory nerve, each tiny electrode or combination producing a characteristic pitch. The patient found that he could recognize gross differences between speech sounds and also identify simple tunes when electrical stimuli were presented through the electrodes.

This investigation was designed primarily to evaluate two aspects of perception: (1) the resolution obtainable by discrete stimulation of several small populations of auditory nerve fibers; and (2) differences between precisely controlled electrical stimuli and the more indirect or induction coil-activated stimuli used by many investigators in the past. It has been highly important in clarifying many of the previously controversial problems. If studies in line with this approach are continued and certain difficulties can be resolved, then the development of an artificial end organ may well become an actuality.

Noise sensitivity linked to sex

Studies into the association between noise and hearing loss in industry, a major occupational problem, have brought out some surprising findings this past year. It has been demonstrated that the protective difference in the ear muscles of

women makes them better than men for certain jobs in industry. Women are able to work at higher noise levels than men without suffering permanent hearing loss and can also hear higher tones above such noises more easily than men.

New technique favored with deaf children

The development of skill in written language remains an area of major concern for teachers of the deaf. Results of experiments in the short-term training of deaf children through visually-presented program materials give promise of solving this problem. On the basis of one study, it appears that training in short-term memory for small units of meaningful language, visually presented, assists the deaf child in establishing memory traces for language patterns. The results of this study has implications for application with other populations, for example, the neurological impaired and mentally retarded children.

Rh damage to hearing clarified

Another hearing impairment is one of the more common disorders observed in children who have suffered from neonatal jaundice due to Rh blood incompatibility. For years, studies attempting to describe the site of the lesion causing this hearing impairment have been contradictory. This past year, however, a group of Institute-supported scientists have done much to clarify the subject. Their study results favor the view that the auditory impairment caused by Rh incompatibility is usually cochlear. However, there is a strong prospect that central lesions also occur, either along with the cochlear lesion or independently. This finding has important implications in respect to the type of defect occurring in the child, the behavior he will exhibit, and his specific needs for treatment.

Testing for aphasia simplified

A short examination for asphasia developed this year is providing an important advancement in reliable diagnosis over the whole range of aphasic disabilities. An Institute-supported investigator has designed a diagnostic scale and a severity scale to be used in conjunction with a range of language behavior tests intended to uncover the extent of aphasia impairment in the patients. The Diagnostic Scale specifies the underlying physiological process, summarizes the critical information obtained from each test section, and presents an overall view of the pattern of impairment in each patient. The Severity Scale estimates the abilities remaining in each language area and the level at which performance breaks down. It indicates what can be expected of the patient at a given time as well as the functional limitations imposed by aphasia.

FUTURE PLANS

Future plans within the Institute's intramural program call for a broad-based increased research effort into the problems of neuro-otology, including the establishment of a new Branch to specifically deal with this area. This new unit will permit a multidisciplinary research effort not easily available at the existing medical centers.

REGENERATION IN THE NERVOUS SYSTEM

Regeneration in the nervous system differs from regeneration of other tissues. The total number of nerve cells in the brain and spinal cord are formed soon after birth. From that time on, the brain grows through an increase in the size of nerve cells, the number of nerve fibers, and through the growth of supporting cells or glia. If a nerve cell dies, it is not replaced. However, if the nervous tissue is cut, it heals the same way skin or muscle does—the adjoining cells uniting to form solid tissue.

To understand regeneration in the nervous system, one must understand the anatomy of the nerve cell. The cell is composed of a cell body containing its nucleus, and many projections, some of great length. There are two kinds of projections; those that carry messages into the cell body, known as dendrites; and those which carry messages from the cell, known as axons. When a nerve axon or dendrite is cut, the part separated from the cell body dies. Restoration of function occurs when the cell projection regrows. There are two problems in regeneration; the cell process growing out must cross the gap made by the injury and then find the proper channel in which to grow. It must then grow along this channel and unite to the proper end organ so that it can function.

In general, the problem of regeneration falls into two separate categories: regeneration of the peripheral nerves or the nerves growing from the spinal cord

or brain to parts of the body, and the regeneration within the spinal cord or brain. At the present time successful regeneration is only known to occur in the peripheral nerves.

The problem of regeneration within the central nervous system, the brain and spinal cord, is quite different. The nerve must not only cross the gap but the channel through which it grows and unites with the end organ is not nearly so well defined as in peripheral nerves and the connections are much more diffuse and more complicated to reestablish.

The National Institute of Neurological Diseases and Blindness is supporting some 25 research projects directly concerned with problems of regeneration at a cost of $665,038. In addition, there are some 290 projects being supported in the fields of embryology, morphology, chemistry of metabolism, enzymology, basic biochemistry and endocrinology which relate indirectly to this problem. Funded at a cost of $8,536,972, these projects are developing knowledge relevant to the understanding of the metabolism of growth, or morphology relating to reconnecting of regenerating nerves. Furthermore, the Head Injury Program, currently funded at $750,000, is concerned with injuries of the nervous system, their prevention and cure. It will develop information highly relevant to nerve regeneration.

The total NINDB commitment for study of problems relevant to the regeneration of the nervous system is almost $10 million.

RESEARCH ON REGENERATION IN THE BRAIN

A cut in the brain heals by growth of the supporting cells or glia; the neurones do not seem to grow out or reconnect. Since it is thought that the glia blocks the growing of nerve fibers, if this could be prevented the nerve fibers might grow across the gap. In several projects investigators are studying the reaction of glia to injury of the nervous system to find the factors which stimulate the glia proliferation and scar formation. It has been demonstrated that the administration of the drug Pyromen, in certain lower species, allows nerve fibers to penetrate and cross the glial scar. This reaction is receiving further study.

It is well known that fish and certain lower animals do show regrowth in the brain and central nervous system after injury, but higher vertebrates such as mammals do not. The repair of brain injury is being studied simultaneously in fish and in mammals in an attempt to find and to isolate the factors which influence repair and regrowth in fish. If such factors can be isolated, they might be applied to the mammalian brain. Along this line, scientists in several research projects are investigating substances such as harmones thought to influence naural regeneration.

The problem of getting a nerve cell process to reconnect in its proper position in the brain and spinal cord after it grows across a cut is one of considerable complexity; so far, only equivocal success has been demonstrated in this area. However, if the processes of neurones in the brain can be properly directed, they will grow out and reconnect to serve their proper function. This has been demonstrated with the facial nerve. The cell bodies of the facial nerve are in the brain. They grow out through the facial nerve to inervate the muscles of the face. It has been well demonstrated that after this nerve has been severed either intracranially or extracranially, it can be sutured so that the fibers will grow out to reestablish normal function.

Regrowth of the nerves from the ear and eye into the brain has not been demonstrated in mammals, although it occurs in lower forms such as fish and amphibians.

Although regeneration in the spinal cord is a problem very similar to that in the brain, it is perhaps a little simpler because of the orientation of fiber tracks and possibly less complicated connections. Patients who have had certain parts of their spinal cord cut to relieve pain sometimes show a return of function after many years. Although it has never been proven beyond doubt that this regeneration occurs within the spinal cord, some scientists consider that there is strong presumptive evidence that it does.

The experimental approaches to spinal cord injury and regeneration have been much the same as those in brain injury. Using knowledge gained from peripheral nerve surgery, studies have been made of efforts to control scar formation to allow cuts to be bridged by nerve fibers. In these studies, cuts in the spinal cord were covered with a millipore or silastic shield to prevent ingrowth of either connective tissue or glia cells and to allow the nerve fibers of the spinal cord to grow out to bridge the gap. Millipore shields are placed around the suture line

of repaired nerves to prevent connective tissue from growing between the two nerve stumps. Millipore, a substance with very small holes, allows nutrient materials to pass but not cells. Since millipore may evoke a tissue reaction, a similar material made from silicone or silastic is now being widely used. Millipore and silastic shields have now been used effectively in the treatment of patients. Use of these shields is particularly important in the treatment of war wounds in which peripheral nerve injuries are extremely common.

Although there has been some success in getting the fibers to cross the gap, no regeneration of the spinal cord function has been observed. In other studies, the cut ends of peripheral nerves have been embedded in the spinal cord to bridge the gap. One scientist has reported some success with this method in dogs; however, other workers have not been able to reproduce these experiments successfully.

In the peripheral nerves the major problem of regeneration and restoration of function after injury is to close the gap of the cut, bringing the portion of the nerve connected with the central nervous system or "proximal stump" in apposition to the portion of the nerve away from the brain nervous system or "distal stump." When this is done, the nerve can grow out of the proximal stump and unite with the end organ. The major problem in peripheral nerve repair is to make the environment suitable for the outgoing fibers crossing the gap. Orienting the fibers to the right channel to grow outward is a problem but if done at the time of repair proves fairly satisfactory. If there is a large gap resulting from injury, closing this presents a serious problem.

The regeneration of the nervous system occurs in fish, amphibia and other lower forms. These lower animals will also regenerate limbs and other parts under certain conditions. The effect of the nervous system on regeneration in these lower forms of life is being studied to add to our knowledge of the interaction between the peripheral organs, skin and the nervous system.

Nerve regrowth usually proceeds at about 1/16 inch per day, but recent research indicates this rate can be advanced by the introduction of certain lipid substances. Desmosterol, a substance which is made during the synthesis of cholesterol, has been particularly effective in speeding regrowth. The overall significance of this phenomenon is not at present understood. It is not known, for example, what relation it has to the other protein growth factors. Attempts are being made to extract and isolate the hormones, chemicals or other agents which influence regenerative growth.

Tissue cultures of nerve cells are also being employed to study nerve growth and regeneration. Through these studies nutrition requirements can be determined. Studies of the formation of myelin and the interaction of glia and nerve cells in tissue culture may give important clues to understanding the regenerative process and factors which affect growth rate.

These are basic studies which are far removed from one easy step to practical application, but they form the building blocks for the final solution of the regeneration problem.

Mr. FLOOD. Thank you very much, gentlemen; 10 o'clock in the morning.

JUSTIFICATION MATERIAL

National Institute of Neurological Diseases and Blindness

Amounts available for obligations

	1967	1968
Appropriation	$116, 296, 000	$128, 633, 000
Transferred to "Operating expenses, Public Buildings Service," General Services Administration	−12, 000	0
Comparative transfer to other accounts	−558, 000	0
Total	115, 726, 000	128, 633, 000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$71, 496, 000		$84, 416, 000		+$12, 920, 000
General research support grants		(6, 288, 000)		(8, 348, 000)		(+2, 060, 000)
Scientific evaluation and planning		(75, 000)		(75, 000)		0
Categorical clinical research centers		(3, 150, 000)		(3, 150, 000)		0
Specialized research centers		(800, 000)		(800, 000)		0
Fellowships		3, 675, 000		3, 805, 000		+130, 000
Training		18, 633, 000		18, 780, 000		+147, 000
Direct operations:						
Laboratory and clinical research	346	8, 485, 000	366	9, 997, 000	+20	+1, 512, 000
Collaborative research and development	228	5, 565, 000	230	5, 980, 000	+2	+415, 000
Biometry, epidemiology, and field studies	80	2, 268, 000	80	2, 305, 000	0	+37, 000
Training activities	3	71, 000	3	72, 000	0	+1, 000
Review and approval of grants	109	2, 180, 000	109	2, 389, 000	0	+209, 000
Program direction	30	871, 000	30	889, 000	0	+18, 000
Total obligations	796	113, 244, 000	818	128, 633, 000	+22	+15, 389, 000
Unobligated balance, reserve		2, 482, 000				−2, 482, 000
Total obligations and balance	796	115, 726, 000	818	128, 633, 000	+22	+12, 907, 000

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Obligations by objects

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	796	818	+22
Full-time equivalent of other positions	60	60	0
Average number of all employees	795	813	+18
11 Personnel compensation:			
Permanent positions	$5,647,000	$5,830,000	+$183,000
Positions other than permanent	390,000	395,000	+5,000
Other personnel compensation	95,000	102,000	+7,000
Total personnel compensation	6,132,000	6,327,000	+195,000
12 Personnel benefits	547,000	560,000	+13,000
21 Travel and transportation of persons	390,000	421,000	+31,000
22 Transportation of things	122,000	132,000	+10,000
23 Rent, communications, and utilities	213,000	235,000	+22,000
24 Printing and reproduction	117,000	177,000	+60,000
25 Other services	1,094,000	1,156,000	+62,000
Project contracts	3,494,000	3,950,000	+456,000
Payment to "National Institutes of Health management fund"	5,428,000	6,218,000	+790,000
26 Supplies and materials	1,184,000	1,487,000	+303,000
31 Equipment	721,000	971,000	+250,000
41 Grants, subsidies, and contributions	93,804,000	107,001,000	+13,197,00
Subtotal	113,246,000	128,635,000	+15,389,000
Deduct quarters and subsistence charges	2,000	2,000	0
Total obligations by object	113,244,000	128,633,000	+15,389,000

Summary of changes

1967 enacted appropriation	$116,296,000
Proposed supplementals:	
Unobligated Balance, reserve	−2,482,000
Comparative transfers to other accounts	−558,000
Transfer to "Operating expenses, Public Buildings Service" General Services Administration	−12,000
1967 total estimated obligation	113,244,000
1968 estimated obligations	128,633,000
Total change	+15,389,000

	Base		Changes to base	
	Positions	Amount	Positions	Amount
Increases:				
A. Program:				
1. Research grants	0	$71,496,000	0	$12,920,000
2. Fellowships	0	3,675,000	0	130,000
3. Training	0	18,633,000	0	147,000
4. Laboratory and clinical research	346	8,485,000	20	949,000
5. Collaborative research and development	228	5,565,000	2	394,000
6. Biometry, epidemiology, and field studies	80	2,268,000	0	31,000
7. Training	3	71,000	0	1,000
8. Review and approval	109	2,180,000	0	26,000
9. Program direction	30	871,000	0	15,000
Subtotal, program increases			22	14,613,000
B. Payment to "National Institutes of Health management fund" for centrally furnished services:				
1. Laboratory and clinical research		3,753,000		570,000
2. Collaborative research and development		309,000		25,000
3. Biometry, epidemiology, and field studies		109,000		7,000
4. Review and approval		963,000		184,000
5. Program direction		290,000		4,000
Subtotal payment to management fund				790,000
Total program increases			22	15,403,000
Decreases:				
1 less day of pay				−14,000
Total decreases				−14,000
Total net changes requested			+22	+15,389,000

EXPLANATION OF CHANGES

Research grants.—The net increase of $12,920,000 includes $10,860,000 for support of the regular programs and $2,060,000 for general research support, grants.

Fellowships.—The increase will be for increased stipend cost and a program increase of 7 postdoctoral awards. The total dollar increase is $130,000.

Training grants.—The increase of $147,000 will provide continued support of the graduate training grants program in the various fields of neurological and sensory disorders.

Laboratory and clinical research.—The program increase of $942,000 will provide supporting costs for the new building and the support of 20 positions required for the expanded programs of intramural research.

Collaborative research and development.—The program increase of $390,000 will support two new positions and continued research in the fields of head injury, slow latent and temperate viruses and other degenerative disorders of the central nervous system.

Biometry, Epidemiology and field studies.—The increase of $30,000 will provide additional logistic support for the programs established in 1967.

Review and approval of grants.—The increase of $25,000 will provide continued support of the staff required for the review and analysis of the grants programs of this Institute.

Program direction.—The increase of $14,000 will provide for additional support of administrative staff in the Office of the Director.

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.

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 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."

Explanation of transfers

	1967 estimate	Purposes
Transferred to:		
Comparative transfer to other accounts	$558,000	Redistribution of the National Institute of Health Management Fund.
"Operating expenses, Public Buildings Service," General Services Administration.	12,000	Transfer of rental costs to GSA.

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$61,103,000	$71,963,000	+$10,860,000
Special programs	10,393,000	12,453,000	+2,060,000
Total research grants	71,496,000	84,416,000	+12,920,000

INTRODUCTION

The National Institute of Neurological Diseases and Blindness supports research grant programs which include research projects, research program projects, outpatient clinical research projects, clinical research centers, and cerebrovascular and head injury planning grants. The primary objectives of these diversified types of grants are the identification, stimulation, and support of essential research on problems related to the diagnosis, treatment and prevention of diseases of the nervous system, the eye and the ear, and human communication. Some of these diseases are among the major causes of death in the United States (stroke, head injury) or are common causes of permanent disability (epilepsy, paralysis, blindness, deafness, loss of speech). They include diseases of the young (cerebral palsy, epilepsy, aphasia, paraplegia, retinal detachment), and of the aged (stroke, brain tumor, parkinsonism, glaucoma, cataract, otosclerosis). The research grant program of this Institute is extending the crucial role already played in providing the research information, technology, and instrumentation required for a nationwide effect against these major causes of death and disability.

PROGRAM PLANS FOR 1967 AND 1968

The budgets for 1967 and 1968 continue to reflect 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.

In fiscal year 1967, approximately 1,531 research projects totalling $61,103,000 will be awarded by the Institute. With the funds requested for 1968, the Institute will award approximately 1,674 research projects totalling $71,963,000.

Of the total increase for 1968, $11,835,000 will be used to meet the rising costs of on-going or non-competing research projects. This research will continue the emphasis in fields of epilepsy, vision, brain injury, speech and hearing, and stroke. There are four major mechanisms of grant support utilized by the Institute to accomplish its research program objectives; these are:

1. Research project grants

In fiscal year 1967, special emphasis is being given to studies of head injury, epilepsy, glaucoma, stroke, and deafness. In addition, national cooperative programs in the planning stage in 1966 were launched on a pilot basis in two major research areas: (1) the natural history, diagnosis and treatment of epilepsy; and (2) the prevention of stroke in patients witb high blood pressure. The program of outpatient clinical research units which was launched in the areas of vision and of human communications (speech and hearing) will be extended to the cerebrovascular area in 1968. Much is yet to be learned regarding the care of ambulatory patients with paralysis and/or aphasia due to cerebrovascular damage.

2. Categorical clinical research centers and program projects

Neurological and sensory disease clinical research centers and program projects provide the research resources and support for selected multidisciplinary clinical research teams engaged in coordinated attacks on the major problems of death and disability involving the nervous system or special senses of vision or hearing. These research teams are organized on either an institutional or multi-institutional (regional) basis and enable investigators in key disciplines to assist each other in developing and testing the new principles and methods which must be perfected to stop the continuing increase and progression of dreaded disorders such as stroke, epilepsy, head injury, blindness, and deafness. During 1967, three additional centers were initiated in the brain research area, two in the areas of stroke, one in the eye research area, and one in the deafness and

human communication area, making a total of 50 active clinical research centers. An additional five centers focusing on major clinical areas are ready to be launched in fiscal year 1968.

3. Outpatient clinical research units

The program of outpatient clinical research units originally launched in two selected areas, disorders of vision and disorders of hearing, speech and human communication, has been extended to include cerebrovascular disorders. In 1968 eleven additional outpatient clinical research projects will be initiated, three on disorders of vision, four on disorders of hearing and human communication, and four on cerebrovascular disorders.

4. Specialized research centers (planning grants)

Clinical center planning grants are awarded for planning the development of additional clinical research centers on important problems of national need. During 1967, planning grants for head injury research as a result of brain damage were initiated on a pilot basis as well as one additional planning grant for Cerebrovascular Centers. An additional six planning grants in head injury research and two in the cerebrovascular area will be initiated in 1968. In research fields of great clinical significance such as head injury and cerebrovascular disease, the Institute can help to mobilize the research resources of the nation to reduce and eventually overcome the consequences of these disabling afflictions by assisting in the development of research teams in newly evolving research centers throughout the nation.

During fiscal year 1968, special emphasis will be given to the following areas of neurological and sensory disease research:

(a) Vision

In the United States over 400,000 people are legally blind, one million have visual impairment so severe they cannot read a newspaper, 300,000 are handicapped to the extent they cannot work, and 3,500,000 have only partial vision. In view of the magnitude of the problem, the Institute is making every effort to develop a complete program for eye research and training to determine the cause, prevention, treatment, and remediation of blindness and visual disorders.

In November 1964 an ad hoc Subcommittee on Vision and Its Disorders was established on the recommendation of the 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 exciting research leads." The report of that expert panel is now available as a basis for the planning and development of additional national activities in this important area. The Institute has now established a permanent Subcommittee on Vision and Its Disorders and is considering the development of a Teacher-Investigator Award Program to strengthen the teaching and clinical investigative aspects of ophthalmology. Some 24 other recommendations also are under consideration. Volume II of the report, containing scientific status papers which provide a comprehensive scientific review of the fields of vision and blindness, is now being made available to the scientific community. Implementation of these recommendations will enlarge and strengthen the program which the National Institute of Neurological Diseases and Blindness has developed for eye research and training.

In addition to the program of individual research projects for the study of blindness, the Institute also supports eye clinical research centers. These centers mobilize a national broad scale attack on visual disorders through the development and application of multidisciplinary approaches to these complex problems.

Support is now being provided for 9 clinical research centers for blindness and visual disorders, each concentrating on special clinical problems such as, cataract, glaucoma, disorders of the cornea, infections of the eye, 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 through 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 visual outpatient clinical research program initiated on a pilot basis in 1966 and 1967 will be expanded. Heretofore, the participation of outpatients with visual disorders in research has been limited by inadequate facilities. Since a large proportion of individuals with vision problems are treated on an outpatient

basis, this meant that valuable clinical material was lost to research. It is already clear that the visual outpatient clinical program will be highly successful in correcting this situation as well as in providing focal points for improved clinical research in all geographic areas of the nation.

(*b*) *Head injury*

Head Injury Clinical Research Centers are complex, interinstitutional, interdepartmental or interdisciplinary programs which often require careful planning involving a major investment in time and effort of both clinical investigators and institution officials. Many institutions found it difficult to prepare proposals for Clinical Research Centers in this area without financial assistance for adequate planning. Thus, a program of specialized center awards (planning grants) for Head Injury Clinical Research Centers was initiated in 1967. This program will be expanded in 1968. Pilot programs, which will already have been started with planning grants, will be expanded and converted into Clinical Research Centers. These Centers will concentrate their efforts on various aspects of the head injury problem such as its epidemiology, the physical forces involved in causing head injury, improved diagnostic and therapeutic procedures, the physiological consequences of head injury, the function and structure of the blood-brain barrier, and the problems of cerebral edema.

(*c*) *Stroke*

Stroke is one of the most common causes of death and not infrequently strikes at a time when the individual is at the peak of his career. For those who do not die, the disease usually means a life of physical disability and mental incapacity. Aphasia, paralysis, and incontinence are the too often tragic consequences of stroke.

As in the case of all medical problems, prevention is the most desirable objective. This requires the development of tests and methods to detect diseases and narrowed blood vessels of the brain in time to prevent complete obstruction. Ways to re-open clogged cerebral vessels and to replace vessels which are diseased beyond repair must be devised and improved; methods for improving collateral circulation to areas not receiving adequate blood are being identified.

The research clinic, which actually works with patients of this kind year after year, is the site to which we must look for important developments in this area. Sixteen clinical research centers for stroke research are presently being supported in 1967, of which 7 are in the planning stages. With the assistance of planning grants, efforts will continue to encourage the development of stroke clinical research centers in additional geographic areas and in institutions which have clinical material that otherwise would not be utilized, but which lack the extensive financial resources required to organize one of these complex centers without assistance. Also, support for outpatient clinical research centers in this area, which was begun in 1967, will be extended in 1968. This is especially important because these ambulatory patients frequently are the best source of information on the early diagnosis of stroke and on the mechanisms that can restore an adequate functional state.

These clinical research centers and outpatient units constitute the main thrust of the Institute's attack on the stroke problem. Much basic laboratory research is still required and needs to be supported: the clinical research center program, however, provides the means by which laboratory findings about the causes, the epidemiology, the treatment, and the prevention of stroke are translated into clinically-used tools.

(*d*) *Disorders of human communication (hearing, language, and speech)*

An ad hoc Task Force on Disorders of Human Communications had been organized by the Institute to review the present state and the problems of communicative disorders and to advise the Institute in regard to needed future programs.

Communicative disorders are somewhat unusual in that there is a growing feeling on the part of experts that many aspects of such disorders can be corrected primarily, if not solely, by early treatment and education. For this reason, it is especially important that these disorders be detected and diagnosed as early as possible before they become firmly established and corrective measures

will be limited in effectiveness. The urgency of early detection makes the participation of medical research and public health personnel of the greatest importance.

For this reason, it is especially necessary that clinical research centers be established and strengthened to provide for research on the diagnosis and treatment of these diseases and for the training of professional personnel. As indicated above, these centers must be multidisciplinary and should include investigators in as many aspects of human communication as possible. 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. Therefore, this was one of the first areas to which the concept of outpatient clinical research units was applied. This activity will be gradually expanded in order that full advantage be taken of the clinical material available in every region of the country.

(*e*) *Muscular dystrophy*

Muscular dystrophy is a very discouraging group of diseases in which the muscles gradually waste away. Available treatments are so poor that many physicians feel any kind of treatment at the present time is useless. Perhaps the saddest aspect is that one type of the disease occurs in children of early school age, particularly boys. Spontaneous temporary remissions make it very difficult to evaluate the effect of therapy accurately.

Several years ago a group of investigators from several institutions requested support for a cooperative study to identify the metabolic and genetic defects which are basic to these disorders. However, the requests were disapproved because they would not meet the strict criteria for a carefully controlled study. Following this, a small technically expert steering committee was appointed which received modest grant support to conduct workshops to develop an adequate protocol. After two years of painstaking work and efforts to resolve crucial problems of research design and technique, the committee is now formulating a critical research plan which can be used successfully by a small group of cooperating institutions. It is expected that grants to support this cooperative study of muscular dystrophy will be activated in 1968.

Research grants program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
Chronic neurological disorders of childhood	$8,690,000	$9,554,000	+$864,000
Chronic neurological disorders of aging	2,066,000	2,545,000	+479,000
Cerebrovascular disorders	4,834,000	5,709,000	+875,000
Epilepsy and related paroxysmal disorders	2,568,000	3,095,000	+527,000
Sclerosing disorders	2,930,000	3,563,000	+633,000
Muscular and neuromuscular disorders	3,125,000	3,693,000	+568,000
Infectious neurological disorders	310,000	474,000	+164,000
Accident and injury	1,889,000	2,333,000	+444,000
Tumors of the nervous system	894,000	998,000	+104,000
Other neurological disorders	11,301,000	13,133,000	+1,832,000
Disorders of vision	11,900,000	14,039,000	+2,139,000
Disorders of hearing and equilibrium	5,051,000	6,164,000	+1,113,000
Disorders of speech and other higher CNS functions	1,685,000	2,095,000	+410,000
Other sensory disorders	2,260,000	2,673,000	+413,000
Noncategorical	1,600,000	1,895,000	+295,000
Subtotal	61,103,000	71,963,000	+10,860,000
General research support grants	6,288,000	8,348,000	+2,060,000
Categorical clinical centers	3,150,000	3,150,000	0
Planning grants	800,000	800,000	0
Scientific evaluation and planning	155,000	155,000	0
Total research grants	71,496,000	84,416,000	+12,920,000

Distribution of research grants

	1967 number	Estimate amount	1968 number	Estimate amount	Increase or decrease	
					Number	Amount
1. Noncompeting continuations	999	$31,578,000	1,160	$43,413,000	+161	+$11,835,000
2. Competing projects	532	22,559,000	514	25,450,000	−18	+2,891,000
3. Supplementals	(213)	6,966,000	(208)	3,100,000	(−5)	−3,866,000
4. Subtotal regular program	1,531	61,103,000	1,674	71,963,000	+143	+10,860,000
5. General research support grants	0	6,288,000	0	8,348,000	0	+2,060,000
6. Scientific evaluation	(5)	155,000	(5)	155,000	(0)	0
7. Categorical clinical research centers	(50)	3,150,000	(55)	3,150,000	+(5)	0
8. Specialized research centers	(7)	800,000	(8)	800,000	+(1)	0
9. Total research grants	1,531	71,496,000	1,674	84,416,000	+143	+12,920,000

FELLOWSHIPS

Total fellowships:

1967 estimate	$3,675,000
1968 estimate	3,805,000
Increase or decrease	+130,000

INTRODUCTION

The research fellowship programs of the NINDB include postdoctoral fellowships and research career awards. These programs provide the financial support necessary to make it possible for scientists and scientist-clinicians to become qualified for research on problems of disease of the nervous system, vision, hearing, and human communication. A group of scientists highly skilled in diversified fields such as neuroanatomy, neurophysiology, neuropathology, audiology, biophysics, ophthalmology, and otolaryngology 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 IN 1967 AND 1968

Postdoctoral fellowships

Postdoctoral fellowships provide the financial support enabling young scientists having just completed doctoral training to obtain the advanced, specialized training required for investigation of diseaess of the nervous system, vision, hearing, and human communication.

In 1968, the postdoctoral fellowship program is expected to be maintained at approximately the same level as in 1967, with continuing emphasis on training in scientific fields relating to epilepsy, head injury, cerebrovascular disease, vision, and human communication.

Career development awards program

Career Development Awards assure salary support over a 5–10 year period for selected young scientists and scientist-clinicians who have completed their research training and who have shown outstanding aptitude for research. It provides them with an opportuntiy to develop a chosen line of research and to become established as independent investigators. These awards are particularly important for the well-trained scientist-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 of this type 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 Fellowship program for the National Institute of Neurological Diseases and Blindness, 81 percent or $105,000 will be applied to the career development program.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
a. Noncompeting	89	$2,009,000	104	$2,442,000	+15	+$433,000
b. Competing	45	535,000	49	571,000	+4	+36,000
2. Supplementals	(11)	9,000	(12)	10,000	+1	+1,000
3. New grants	128	1,122,000	111	782,000	−17	−340,000
4. Total fellowships	262	3,675,000	264	3,805,000	+2	+130,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Postdoctoral	137	$900,000	144	$900,000	+7	0
2. Research career:						
a. Career	13	350,000	13	375,000	0	+$25,000
b. Development	112	2,425,000	107	2,530,000	−5	+105,000
3. Total fellowships	262	3,675,000	264	3,805,000	+2	+130,000

Training Grants

Total training grants:

1967 estimate	$18,633,000
1968 estimate	18,780,000
Increase or decrease	+147,000

INTRODUCTION

The Training Grants program of the National Institute of Neurological Diseases and Blindness provides funds to institutions to aid in establishing, improving, or expanding training programs to prepare scientists and scientist-clinicians for careers in research and academic medicine, 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. Training programs in the area of cerebrovascular disease also have the important objective of preparing clinicians for careers in the clinical aspects of cerebrovascular disease.

In 1967 the Institute expects to support approximately 296 training programs, and through these programs provide training for about 1,790 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; however in terms of meeting even a minimum level of national needs, the program is just beginning to achieve its objectives.

The responsibility for future advances in understanding, preventing, and treating successfully the neurological and sensory disorders rests essentially with this group of scientists and scientist-clinicians who are trained as leaders in teaching and research.

Program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
1. Neurology	$4,937,000	$4,734,000	−$203,000
2. Ophthalmology	2,997,000	2,997,000	0
3. Otolaryngology	2,627,000	2,627,000	0
4. Auditory physiology	75,000	75,000	0
5. Communicative disorders	255,000	255,000	0
6. Medical audiology	210,000	210,000	0
7. Neuroanatomy	238,000	238,000	0
8. Neurochemistry	202,000	202,000	0
9. Neuropathology	670,000	670,000	0
10. Neuropharmacology	250,000	250,000	0
11. Neurophysiology	646,000	646,000	0
12. Neuroradiology	214,000	214,000	0
13. Neurosurgery	508,000	508,000	0
14. Experimental neurosurgery	107,000	107,000	0
15. Ophthalmic basic science	203,000	203,000	0
16. Otolaryngology and audiology	178,000	178,000	0
17. Otological pathology	86,000	86,000	0
18. Pediatric neurology	458,000	458,000	0
19. Medical neurology and public health	43,000	43,000	0
20. Sensory physiology	177,000	177,000	0
21. Speech pathology	132,000	132,000	0
22. Speech pathology and audiology	135,000	135,000	0
23. Vision psychophysiology	10,000	10,000	0
24. Cerebrovascular	100,000	450,000	+350,000
25. Scientific evaluation and planning	175,000	175,000	0
Total graduate training grant program	15,633,000	15,780,000	+147,000

Traineeships, program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
1. Neurology	35	28	−7
2. Ophthalmology	27	26	−1
3. Otolaryngology	5	5	0
4. Audiology-speech pathology	4	4	0
5. Biochemistry	8	8	0
6. Biophysics	7	7	0
7. Neuroanatomy	9	9	0
8. Neurochemistry	4	4	0
9. Neurocytology	6	6	0
10. Neuroendocrinology	5	5	0
11. Neuropathology	16	15	−1
12. Neuropharmacology	7	7	0
13. Neurophysiology	21	20	−1
14. Neuroradiobiology	14	14	0
15. Neurosurgery	3	3	0
16. Ophthalmic pathology	13	13	0
17. Pediatric neurology	49	49	0
18. Physiological psychology	3	3	0
19. Sensory physiology-pathology			
(Vision)	5	5	0
(Otolaryngology)	3	3	0
20. Speech and Hearing Mechanisms	4	4	0
21. Virology-Immunology	7	7	0
22. Cerebrovascular	40	43	+3
Total	295	288	−7

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Continuations:						
(a) Noncompeting	207	$10,152,000	209	$12,100,000	+2	+$1,948,000
(b) Competing	166	4,932,000	166	4,352,000	0	−580,000
Supplementals	(45)	341,000	(35)	213,000	(−10)	−128,000
New grants	218	3,033,000	190	1,940,000	−28	−1,093,000
Scientific evaluation and planning	(5)	175,000	(5)	175,000	0	0
Total training grants	591	18,633,000	565	18,780,000	−26	+147,000
Graduate	296	15,458,000	277	15,605,000	−19	+147,000
Traineeships	295	3,000,000	288	3,000,000	−7	0
Scientific evaluation and planning	(5)	175,000	(5)	175,000	0	0
Total training grants	591	18,633,000	565	18,780,000	−26	147,000

LABORATORY AND CLINICAL RESEARCH

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	346	$2,979,000	366	$3,113,000	+20	+$134,000
Other expenses	--------	5,506,000	--------	6,884,000	--------	+1,378,000
Total	346	8,485,000	366	9,997,000	+20	+1,512,000

Program plans for F.Y. 1967

CLINICAL RESEARCH

Medical neurology

Investigations in medical neurology emphasize multifaceted and integrated studies of patients with neuromuscular disease. Applied directly to the patients are the newest aspects of the basic research techniques of histocheimstry, biochemistry, immunology, electronmicroscopy, tissue culture and autoradiography. The interrelating of these basic techniques and applying them to study the dynamic molecular aspects of neurologic disease is our newly developing approach. Specific abnormalities of protein metabolism have been identified and/or further clarified in such neuromuscular diseases as several forms of muscular dystrophy, myasthenia gravis, and peripheral neuropathy. The objective is to identify and treat specific biochemical abnormalities in both genetically inherited and acquired neurologic disorders. An expanding program is concerned with investigating amyotrophic lateral sclerosis by basic clinical research techniques as well as clinical therapeutic trials.

Radiographic studies are concentrating on new instrumentation and techniques for the demonstration of brain tumors and other neurologic disorders. Basic pharmacologic investigation is concerned with the molecular aspects of the link between excitation and muscle contract in order to understand abnormalities thereof.

Surgical neurology

Investigations are conducted on epilepsy, head injury, involuntary movements, cerebral palsy, cerebral degeneration in children, effects of surgery on the brain, effects of flow temperature on the brain, disturbances of language and memory, and in a variety of surgical techniques.

Head injury and its accompanying brain damage are important causes of death and disability which are now being investigated. Through the 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 consequence of head injury. The occurrence of brain swelling within the closed cerebral cavity greatly aggravates the results of injury. For this reason, modification of brain swelling would be an important contribution. Investigations of the disturbed permeability of the blood brain barrier through the use of radioactive tracers and other specialized techniques are being conducted.

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, and in an equally new technique, anticarcinogenic drugs are instilled directly into the brain cavities of the afflicted patient.

The physiological mechanisms of involuntary movements and epilepsy are studied by electronic techniques, and the clinical investigations in epilepsy, brain tumors and involuntary movements are supported through experimental surgery in animals, which are also used as a means for studying the effects of surgery itself.

Ophthalmology

Studies of the mechanisms through which the visual image is converted to coded messages within the eye and thus interpreted within the central nervous system are progressing. 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 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 characteristics of that disorder, on pharmacological and physiological studies and the evaluation of the effectiveness of therapeutic agents in patients.

The approach to diseases of the cornea centers upon biochemical investigations of the nature of the collagenous supporting matrix of various parts of the eye. Such knowledge is esesntial to an understanding of the mechanisms through which the cornea becomes cloudy under disease.

The therapy of inflammations of the eye 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. Using fine needle electrodes in animal and human subjects, the electrical activity of the brain cells is being recorded under normal and abnormal conditions. Such knowledge is essential to an understanding of the deviations of electrical activity underlying the epileptic seizure.

Other interests verge on the mechanisms at the basis of abnormal motor behaviors such as those occurring in Parkinson's disease and related disorders.

LABORATORY RESEARCH

Neuroanatomical sciences

This laboratory conducts investigations of the mysterious processes which guide the growth and development of the nervous system, sense organs, and motor structures within the developing embryo, and of the mechanisms whereby these normal processes may be disturbed by toxic drugs, injury or disease.

These are the processes underlying such devastating congenital malformations as microcephaly, hydrocephalus, meningocoele, congenital cataract and glaucoma. They also relate to problems of regeneration of the injured nervous system.

In addition, this laboratory conducts pioneering investigations of the nervous pathways for hearing, and of the development of the organ of hearing.

Biophysics

The work is directed generally toward elucidating 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 the information carrying impulse. The approach combines laboratory investigations on single axons, artificial membranes, and membrane models using mathematical analysis with the aid of computers. The experimental work is extending and improving the concept of fast and slow channels by which several different univalent positive ions cross the squid axon membranes and the role of divalent positive ions in blocking them. New experimental and theoretical methods and techniques are being developed to determine the size and number of these channels and to describe the processes which open and close them.

Neurochemistry

The employment of newly developed analytical techniques for the investigation of the chemical structure of the brain in health and disease underlies much of the ongoing research in neurological and sensory disorders. For this reason, the Laboratory of Neurochemistry serves as a focal point for extensive collaborative work both inside and outside of the Institute. The laboratory is using new techniques to study the chemical concomitants of nerve activity and excitability, to study energy requirements of fluid and ion transport across membranes, and to investigate alterations of protein and amino acid components of the brain in health and disease. 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 two of these devastating neurological disorders—Gaucher's Disease and Niemann-Pick's Disease.

Molecular biology

Many disorders of the brain and sense organs are the result of genetically determined deviations of chemistry and/or structure. New discoveries demonstrate that these deviations result from abnormalities of the genetic material (DNA), i.e. large complex molecules contained within the chromosomes of the living cell. Solution of these problems requires an elucidation of the mechanisms through which the genetic material may be damaged, and the processes whereby deviations of this material lead to developmental alterations of the body. These molecular biology studies are concerned with an explanation of these basic biological problems in molecular terms. Working primarily with bacteria and viruses that attack them, the mutagenic and chromosomal breaking alterations of DNA produced by various chemical and physical agents are studied, and the alterations in nucleic acid and protein synthesis and function resulting from modifications of the genes and leading to developmental malformations are analyzed. These studies are essential to the understanding of the mechanisms of inborn errors of metabolism and other genetically determined disorders.

Neuropathology

The Laboratory of Neuropathology is currently engaged in research on the functional and morphologic relationship between nerve cells and other nonneuronal, or glial, elements in the brain. Different animal species subjected to

transection of a peripheral nerve are being studied in order to ascertain (1) the sequence of neuronal changes and (2) the incidence of mitotic cell division, both of which have been found to vary with age and species. A correlation between degree of neuronal change and incidence of mitosis in cells situated on the outside of blood vessels is demonstrable, suggesting that induction of mitosis is controlled by the functional condition of the nerve cell. Since the ensuing daughter cells become transformed to microglial cells, these series of investigations have provided new information about the origin and formation of these cells and about the interdependence of microglia and nerve cells. In addition to age and species differences, the effect of homeostatic changes, caused by administration of hormones, drugs, etc., is being scrutinized in an attempt to clarify factors involved in this interdependence.

Neurophysiology

Synaptic mechanisms continue to be a major subject of study. The manner in which unitary events are combined to for the larger evoked synaptic potentials has been elucidated for spinal motoneurons. Afferent fibers from muscle spindles make monosynaptic connections with motoneurons which are widely distributed over the surface of the motoneurons. Different nerves may have somewhat different patterns of termination and the interaction between synaptic activity produced by stimulation of different nerves is influenced by the dendritic distribution of their terminations. Each nerve ending may produce from one to several unitary, quantal synaptic events when the ending is activated by an action potential. Even synaptic contacts in the periphery of the dendritic tree provide a significant excitatory depolarizing effect in the cell soma near the spike trigger zone.

Sensory processing in the cochlear nucleus has been studied in anesthetized and in unanesthetized decerebrate cats. Relatively simple sensory mechanisms predominate in the cochlear nucleus in general, although differences between the dorsal and ventral divisions of the nucleus have been demonstrated. A marked alteration in response patterns of neurons in the primary auditory nucleus is produced by barbiturates, emphasizing the distortion in neural properties introduced by this class of drugs.

Work is going forward which invovles analysis of electrical signs of altered metabolic and blood-brain barrier transport in the brain. The brains of the cat and the Rhesus monkey have shown striking reactions to changes of pH of the blood and to blood flow. These factors are sensitive to injury and work on hypoxic and concussion is being continued in collaboration with the Surgical Neurology Branch.

Perinatal Physiology

The Laboratory of Perinatal Physiology in Puerto Rico carries on studies in comparative neurology, physiological psychology, neurochemistry, and social and instinctual behavior. The main focus of attention, however, is in the causation and prevention of cerebral palsy and mental retardation. It has been possible to mimic in monkeys almost all the classical pictures of cerebral palsy as it afflicts man.

Studies are carried out on the chemical changes occurring in the blood stream and brain of the asphyxiated infant monkey. Studies relating to blindness include investigations of the indentity and locus within the nervous system of processes involved in visual perception, memory and learning. Other studies record the electrical activity of single nerve cells of the visual mechanism of the primate brain.

The adjustments of the primate nervous system, and the reactions of damaged animals under more normal conditions are under investigation in free-ranging monkey colonies on several small off-shore islands. In addition to supporting scientific studies of the monkey, these facilities also serve as a source of unique populations of the rhesus monkey. The uniqueness derives from their known source of origin, and their prolonged isolation from disease contact.

Its facilities include a main laboratory at the U.S. Public Health Service Outpatient Clinic in San Juan, 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 built on the grounds of the Puerto Rico Medical Center, with completion expected in 1969. In addition, steps are being taken to transfer land from another federal agency on which it is intended to establish an experimental primate compound facility several miles away, and complementary to the new facility at the Medical Center.

Program plans for 1968

January 1968, the Institute expects to occupy the new facility in Bethesda, which for NINDB totally, provides approximately an additional 73,000 net square feet. Within this, two new programs will be created—Neuro-otology and Neurological Control—and laboratories now in the Clinical Center will relocate and expand in the new building. In addition the clinical branches remaining in the Clinical Center will be able to expand because of space vacated by the laboratories moving to the new facility.

Neuro-otolaryngology

In 1968 the Institute plans to establish a new Neuro-otolaryngology 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. There are broad and basic problems, therefore, which go uninvestigated because these problems require an interspecialty team committed to problems that cut across the traditional foci of interests in the communicative processes. The type of research activity visualized for this Branch is much broader than that which is possible in the usual medical research facility. Human communication is a multifaceted product of complex neurological processes. Consequently, the scientific evaluation of both normal and abnormal communicative processes requires multidisciplinary research. A Neuro-otolaryngology Branch will have two missions; (1) to conduct long-range, multidisciplinary research on the normal processes of the sensory, central and efferent mechanisms which are used for human communication, and (2) to carry out similar research on the identification, manifestations and amelioration of aberrations in these mechanisms.

In addition to research and training, the Neuro-otolaryngology Branch would provide a consultation service, particularly in otolaryngology and audiology both within this Institute and the Clinical Center at Bethesda, generally.

Neurological control

Neurological science has progressed to a point where it is now possible to obtain precise knowledge of the sensory reception of information into the nervous system and analysis of this information within the brain. Newly developing computer techniques are providing the capability for a much more sophisticated analysis of the nervous system and its functioning. To exploit these new capabilities, the Institute plans to develop within its Bethesda program a Laboratory of Neurological Control. This research unit will develop techniques for nervous system control of external devices (outward information transfer), and methods of external control of the nervous system (inward information transfer). Other investigations will seek to construct mathematical models of information processing in the nervous system and explore the process in depth.

Man has only begun to tap the capabilities of the nervous system. Thus, physicians in the future may not only "key-into" the nervous system to provide aids for the blind and the deaf, they may also "key-out" of the nervous system to bypass the physical restrictions of the handicapped. In normal man, it will be possible to activate remote devices without the necessity for cumbersome movements. One day in the future, information may be transferred directly from the nervous system to a computer without muscular effort. Some scientists predict that this is an inevitable human development, upon which survival of society may depend.

SUMMARY OF INCREASE

Included in this net increase is $942,000 for program expansion as explained above offset by one less day of pay in 1968. There is also an increase of $570,000 for centrally furnished services from the "National Institutes of Health Management Fund".

COLLABORATIVE RESEARCH AND DEVELOPMENT

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	228	$1,340,000	230	$1,380,000	+2	+$40,000
Other expenses		4,225,000		4,600,000		+375,000
Total	228	5,565,000	230	5,980,000	+2	+415,000

ACCIDENT AND INJURY

During 1967 a great deal of the planning necessary to launch an aggressive and expanded program of research into the problem of acute head injury was accomplished and significant steps were taken to initiate such a program. 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. The clinical and basic scientists, from seven countries, participating in the conference identified the following areas as warranting immediate attention: more precise information regarding incidence and prevalence; classification of injuries, and standards of measurement for clinical and research activities; means for prevention or reduction in incidence and severity; establishment of specialized facilities with integrated services for the treatment and investigation of head injuries, which will include sequential studies and rehabilitation, and multidisciplinary research programs; the participation of engineers and physical scientists in these efforts; the utilization of other clinical and experimental laboratories; the support of career scientists; the opportunities afforded by military experience; education and dissemination of information.

The Congress, in September 1966, stated in its appropriation document 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. The pilot phase will take place in the Buffalo, New York, metropolitan area (Erie County), and involves a circumscribed population. Additional research projects involving larger, smaller, and more diverse population groups are being planned.

The compilation of a glossary, by expert consultants, has been completed. This will be useful in multidisciplinary research activities. The same consultants, utilizing updated criteria, will formulate a categorization of head injuries.

The award of several planning grants for clinical research centers concerned with head injury during 1967 should result in the future demand for operational grants for such centers.

Efforts are underway to develop physical and mathematical models simulating human and animal craniocerebral structures, the mechanical loads applied to them, and the responses of these systems, in order to better study and understand the physical forces of head injury.

Longitudinal studies of the effects of head injuries occurring in war situations are being carried out. The initial and partial follow-up data on 1400 U.S. Armed Forces casualties and 100 controls from the Korean campaign are being supplemented by a 15 year follow-up in collaboration with the Veterans Administration. The statistical evaluation of retrospective data on 1100 casualties from World War I is in progress. Comparative studies of the material from World Wars I and II and the Korean campaign will follow. Pilot efforts have been undertaken with the Department of Defense to gather comparable data during the acute phase of combat head injuries from the Vietnam conflict.

EPILEPSY

The pilot phase of a collaborative study of epilepsy coordinated by the Institute and involving four clinical centers is providing the feasibility of a prospective data collection study of all aspects of epilepsy. Upon completion of a pilot phase during 1968 the study will be broadened to include 8 to 12 centers and data on a large population of patients. The study will yield many data heretofore unavailable concerning the natural history of epileptic and related paroxysmal disorders.

In the past decade not a single new anti-convulsant compound has been developed which can be used in the control of epileptic seizures. Current anti-convulsants and other drugs have proven to be only about 60 percent effective in the control of these disorders. With funds made available in 1967 a program of support for anti-convulsant drug development has been planned. In 1968 this program will be continued and strengthened and may possibly include support for field trials and tests of new anti-convulsant compounds.

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 exchanged. During 1967 support of publication of a complete international bibliography on epilepsy is contemplated. In the future this effort can be complemented by the establishment of an information center which can review, store, and disseminate scientific and technical information on epilepsy and basic research related to the 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 healthy development of the nervous system and sense organs. The study relies upon the collaboration of 15 institutions in gathering comprehensive data from pregnant women and their children.

This project, supported by the Institute was conceived and undertaken eight 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 physical defects.

Participating institutions, in addition to Buffalo's Children's Hospital, are the 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.

Project investigators now are assessing data collected on nearly all of the 60,000 pregnancies and resultant babies over the past seven years and more. These data pertain to infections and illnesses experienced by each mother during her pregnancy, the drugs she took, accidents she may have suffered, and other health circumstances surrounding the birth of each child as well as followup data on each child since birth.

Several hundred children born to mothers during the first year of the project, and now seven years or more old, are about to undergo final examinations and will soon complete their participation in the study. Final analysis of the entire data cannot begin unti 1974, however, when the total information goal of the project is complete for all children.

Meanwhile, because the study is prospective rather than retrospective, investigators are finding their Perinatal Research Project data highly valuable where neurological defects have appeared. In these cases, considerable etiological information is readily at hand, as opposed to difficult and often impossible backward searching for information on a child's development.

Project data also have enabled a number of significant findings, to date, revealing or confirming that:

Older mothers—those over forty are most likely to have infants with neurological or psychological abnormalities.

Mothers fifteen years of age or under bear a higher percentage of babies with abnormalities than more mature women do.

Incompetent cervix remains a major high-risk factor in neurological damage and infant deaths.

General anesthesia given the mother during cesarean delivery appears to be related to poor response of the baby at birth.

A marked increase in neurological abnormalities is apparent in premature children. Thirty percent of one-year-old babies with neurological problems were born prematurely.

A wider understanding has been gained of the effects of certain drugs administered during pregnancy.

In addition, collaborating investigators hope to gain new knowledge relating to the role of viruses, radiation toxicity, chemical abnormalities, vascular disturbances, and other factors producing retardation.

The beginning of a new phase of this study may signify the beginning of even greater knowledge of the causes of birth defects as well as later health problems. Eventually, perhaps, these causes will be prevented or eliminated.

Program plans for 1968

With new laboratory space becoming available on January 1, 1968, it is planned to extend to special areas of the project the study of pathological changes in cerebral palsy and the evaluation of the role of infectious agents in neurology disorders of infancy and childhood.

MEDICAL INFORMATION CENTER

Under the leadership of the Office of Program Analysis, the network of specialized information centers to serve the biomedical community is in various degrees of development. The first center concerned with clinical neurological problems is operational, the center on basic neurological sciences is near operational, whereas the center on speech, hearing, and human communications is still in the developmental phase. The newest center concerned with vision and diseases of the eye, recently designated, is getting underway with recruitment and initial planning.

These large information centers, each covering a specialty area, are integrated with each other and with the National Library of Medicine to avoid duplication of effort. While these centers are considered the core of the network, it is planned that they, in addition to their own information analysis activities, will support information analysis satellites at other research centers where specific categorical research programs are underway. A National Advisory Committee for the Information Network will be established in 1967.

Additional information activities, although not directly linked with the network, include the literature alerting service in the area of cerebrovascular disease and stroke which is being continued and expanded to a larger user audience.

SUMMARY OF INCREASES

The total increase includes $25,000 for centrally furnished services of the National Institute of Health management fund and the balance for $390,000 will provide additional funds for two positions and for continuing support in the research fields of head injury, slow latent and temperate viruses and other degenerative disorders of the central nervous system.

BIOMETRY, EPIDEMIOLOGY, AND FIELD STUDIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	80	$1,040,000	80	$1,040,000	0	0
Other expenses	--------	1,228,000	--------	1,265,000	--------	+$37,000
Total	80	2,268,000	80	2,305,000	0	+37,000

Program plans for 1967 and 1968

BIOMETRICS

The major program of this Branch has been to standardize the collection of statistics on blindness and severe vision impairment throughout the United States. For this purpose the Model Reporting Area for Blindness Statistics has been established. Currently, 14 states comprising approximately 19 percent of the nation's population are included in the Model Reporting Area. During 1967 four additional states are in the process of preparing blindness registers in compliance with the standards established for the entire Model Reporting Area. When these states are added to the Model Reporting Area, approximately one-third of the nation's population will be covered. In addition, studies validating the accuracy of data reported and the completeness of the registry's coverage have been initiated. This program, which for the first time is providing consistent data on the incidence, prevalence, and causes of blindness, has received wide endorsement from volunteer agencies concerned with the problem of vision and vision impairment. The validity of the data is continually being improved by studies of the methodology whereby such reporting systems can be established and maintained in fields other than blindness or vision impairment. This will

allow more states to prepare blindness registers within their jurisdictions and subsequently increase the coverage and accuracy of the Model Reporting Area's statistics. Validation studies concerning the coverage of the registers and the accuracy of reported information will continue.

EPIDEMIOLOGY

During 1967 an aggressive program of investigation into the epidemiology of stroke has been launched. The validity of certain mechanisms utilized in reporting cerebrovascular disease deaths is being investigated. In addition research into the method of diagnosis of stroke is being initiated.

Other studies of peripheral neuritis, Bell's palsy, and retrobulbar neuritis and of patterns of multiple sclerosis in the United States and Puerto Rico are continuing.

Genetic studies of selected acute and chronic neurological disorders have been initiated with current emphasis on a series of 200 cases of dystonia musculorum deformans.

A registry of 2,500 Guamanians now living in the United States is completed and related to studies being carried out on Guam, with appropriate laboratory back-up in Bethesda. It is hoped that these investigations will provide more definitive information on the role of genetics in the apparent susceptibility to certain neurological and sensory disorders.

The unique resources available on the island of Guam will be utilized for further investigations of amyotrophic lateral sclerosis and other neurological and sensory disorders with high incidence in that isolated environment. Investigations will be continued to elucidate a possible environmental or genetic factor in the particular ALS/Parkinsonism-dementia complex. The possible occurrence of this disease in non-Chamorro residents of Guam will be subjected to investigations. The possible virological cause of ALS is being studied through the inoculation of presumptive infected material into a variety of animals including primates and domestic farm animals. Also unusual metabolic patterns of glucose and uric acid are being studied in hopes of relating these abnormalities to the neurologic diseases on Guam.

In the laboratory, lymphocytes from patients with multiple sclerosis and other degenerative neurological diseases are underway in order to determine the role of hypersensitivity in these diseases.

Efforts to develop more precise methodology for the early diagnosis of glaucoma has become a major focus of the Section on Ophthalmic Field and Developmental Research. A critical evaluation of methods of tonometry which has been completed as have surveys of selected white and Indian populations in the United States. An intensive investigation of the genetics of eye diseases is underway. This study is utilizing a registry of over 300 pairs of twins all located in the Washington, D.C. area. The examination of these identical and non-identical twins will provide important information regarding the role of an inheritance in glaucoma, myopia, and other eye disorders.

A study of pathologic diseases of the eye has been undertaken and promises to yield significant data concerning the tolerance of the eye and ocular tissue to carcinogens.

Epidemiological investigations of the blood vessels of the eye which are important in the evaluation of cerebrovascular diseases demand more precise instrumentation for measuring and evaluating the characteristics of those blood vessels. The use of television scanning devices and advanced television technology presents a possible avenue of research and development.

SLOW AND LATENT VIRUSES IN NEUROLOGICAL AND SENSORY DISEASE

For the past several years the Institute has been developing a program to search for viruses as a cause of chronic neurological disease such as, multiple sclerosis, amyothopic lateral sclerosis, Parkinsonism and the encephalitides of childhood. The Project of Slow, Latent, and Temperate Virus Infections was established as part of the Study on Child Growth and Development and Disease patterns in primitive cultures in 1961–62. The Institute had long recognized the need for a laboratory whose major mission was to attempt to transmit chronic and sub-acute degenerative diseases of the central nervous system of man to experimental hosts, and in so doing, established 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 is a proven transmissible disease caused by an extremely small filterable agent with an incubation period of three to five years 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; small experimental animals, e.g., mice, guinea pigs, hamsters, rabbits; and avian hosts; and tissue culture cell lines. Such experimentally inoculated hosts would be held in isolation 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 Guamanian, encephalitis, multi-focal leuco-encephalopathy, Schilder's Disease, acute necrotizing leuco-encephalopathy, and ALS material from monkeys from the U.S.S.R.

Eighteen months after inoculation of animals with suspensions of brain tissue from Kuru patients a clinical syndrome strikingly similar to Kuru in humans was observed in a chimpanzee. In subsequent weeks and months, additional chimpanzees, inoculated with Kuru-affected human brain material, have developed disease. The neuropathology is identical to the neuropathology described as occurring in Kuru human brain. In all, six of seven Kuru patients' brains tested have induced disease in eight of nine chimpanzees inoculated. 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. This highly significant development, restricted for the time to chimpanzees, represents the transmission of a human degenerative central nervous system disease to an experimental host with perhaps a genetically influenced disease expression.

These developments necessitated expansion in the number of experimental animals to be inoculated; an increase in the number of species of ape, monkey, and domestic animals in an attempt to broaden the host susceptibility range and to find more readily available and substantially less expensive animals than the chimpanzee; enlargement and significantly improved laboratory and animal holding facilities to insure protection of (a) individual investigators and technicians, (b) the public health environment, and (c) long term program animals in well-controlled isolation. Further, in order to move rapidly in the followup of the program developments, the Institute has proposed the increase of space, both by temporary construction and the use of contracts, with increased 1967 appropriations.

Summary of increases

The increase of $37,000 includes $7,000 for centrally furnished services of the National Institutes of Health Management Fund and $30,000 for additional logistic support.

TRAINING ACTIVITIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	3	$38,000	3	$38,000	0	$0
Other expenses	--------	33,000	--------	34,000	--------	+1,000
Total	3	71,000	3	72,000	0	+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 for 1967 provide for training in otolaryngology, neurology, epidemiology, and neurosurgery; and includes an increase of $1,000 for additional administrative support of the program.

Review and approval of grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	109	$974,000	109	$974,000	0	0
Other expenses		1,206,000		1,415,000		+$209,000
Total	109	2,180,000	109	2,389,000	0	+209,000

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, encumbered 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.

PROGRAM ANALYSIS

The Office of Program Analysis has established a cross-indexed file of all current research in the Institute. This is an operational file for use in planning and answering inquiries. Next year, it will be expanded to include more data about relevant research carried out by other government agencies and private foundations. It will also be expanded in relation to reports relevant to progress in current or long-term projects.

A manpower file is being compiled concerning research in the neurosciences. This file is cross-indexed by a scientist's name geographical location, or by discipline and subject. The principal investigators of the Institute's grantees are entered in this file, and it is being expanded to include all American scientists working in the fields of neuroscience. This is being used to review and update the manpower estimates and training program effectiveness of the Institute.

A review of the data pertaining to the economics of diseases for which the Institute has responsibility has been undertaken, and all information relevant to this problem is being assembled.

A special section of the Office of Program Analysis has been instituted for problems of Vision, Blindness, and Diseases of the Eye, and will be a focal point for information of the Institute activities relating to these problems.

The assembly of information concerning scientific activities of the Institute and progress made by the various scientists supported by the Institute will allow for more detailed evaluation and planning in the forthcoming years.

SUMMARY OF INCREASES

Of the total increase, $25,000 is for additional program support of the institute and the balance, $184,000, is for centrally furnished services of the NIH management fund.

PROGRAM DIRECTION

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	30	$308,000	30	$308,000	0	0
Other expenses		563,000		581,000		+$18,000
Total	30	871,000	30	889,000	0	+18,000

This activity provides support for the Office of the Director, including the professional, administrative, secretarial and clerical staff required for the direction and coordination of all Institute programs, the review of current and proposed operations, and supervision and provision of administrative services on a centralized basis. These administrative functions include also management in the areas of finance, personnel, supply, travel, space utilization, and management analysis.

Included in the net increase is $14,000 for support of administrative cost associated with the expanded programs and $4,000 for centrally furnished services of the NIH management fund.

New positions requested, fiscal year 1968

	Grade	Number	Annual salary
Research:			
Full grade (2)	C.O.		$16,294
Medical officer	GS-15	4	17,645
Scientist	GS-15	2	17,555
Do	GS-14	2	15,101
Mathematician	GS-13	2	12,875
Research chemist	GS-13	1	13,312
Research phychologist	GS-12	2	10,920
Chemist	GS-11	1	9,214
Medical technician	GS-9	1	7,696
Biologist	GS-7	1	6,448
Clerical assistant	GS-7	1	6,448
Biological laboratory technician	GS-5	1	5,325
Clerical assistant	GS-5	2	5,325
Total		20	144,158
Collaborative research and development:			
Supervisory statistician	GS-15	1	17,555
Statistician	GS-14	1	15,101
Total		2	32,656
Total new positions, all activities		22	176,814

WEDNESDAY, APRIL 12, 1967.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. DORLAND J. DAVIS, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DR. JAMES A. SHANNON, NATIONAL INSTITUTES OF HEALTH
DR. JAMES W. COLBERT, ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAMS, 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
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

In thousands of dollars

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	5,600	6,063	6,133
11.3	Positions other than permanent	36	39	51
11.5	Other personnel compensation	129	133	133
	Total personnel compensation	5,765	6,235	6,317
12.0	Personnel benefits	633	704	718
21.0	Travel and transportation of persons	230	270	300
22.0	Transportation of things	56	60	60
23.0	Rent, communications, and utilities	204	198	210
24.0	Printing and reproduction	5	5	5
25.1	Other services	1,005	1,270	1,300
	Project contracts	6,931	9,220	10,900
25.3	Payment to "National Institutes of Health management fund"	4,714	4,976	5,479
26.0	Supplies and materials	1,753	2,000	2,177
31.0	Equipment	493	515	520
41.0	Grants, subsidies, and contributions	55,808	61,809	66,454
	Subtotal	77,597	87,262	94,440
95.0	Quarters and subsistence charges	−18	−18	−18
99.0	Total obligations	77,579	87,244	94,422

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	733	751	764
Full-time equivalent of other positions	4	5	6
Average number of all employees	699	712	720
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	43,326	49,006	52,936
(b) Fellowships	3,424	3,700	4,267
(c) Training	9,058	9,103	9,251
Total, grants	55,808	61,809	66,454
2. Direct operations:			
(a) Laboratory and clinical research	10,969	12,488	13,746
(b) Collaborative research and development	6,142	9,954	11,025
(c) Biometry, epidemiology and field studies	1,120	1,289	1,356
(d) Review and approval of grants	1,241	1,358	1,482
(e) Program direction	335	346	359
Total, direct operations	19,807	25,435	27,968
Total program costs, funded [1]	75,615	87,244	94,422
Change in selected resources [2]	1,964		
10 Total obligations	77,579	87,244	94,422
Financing:			
16 Comparative transfer to other accounts	130	3,250	
25 Unobligated balance lapsing	277	164	
New obligational authority	77,986	90,658	94,422
New obligational authority:			
40 Appropriation	77,987	90,670	94,422
41 Transferred to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−1		
"Operating expenses, Public Buildings Service," General Services Administration (80 Stat. 674)		−12	
43 Appropriation (adjusted)	77,986	90,658	94,422
Relation of obligations to expenditures:			
10 Total obligations	77,579	87,244	94,422
70 Receipts and other offsets (items 11–17)	130	3,250	
71 Obligations affecting expenditures	77,709	90,494	94,422
72 Obligated balance, start of year	36,743	50,606	64,893
74 Obligated balance, end of year	−50,606	−64,893	−81,343
77 Adjustments in expired accounts	−1,189		
90 Expenditures	62,657	76,207	77,972

[1] Includes capital outlay, as follows: 1966, $457,000; 1967, $515,000; 1968, $520,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $5,954,000 (1966 adjustment, −$69,000); 1966, $7,848,000; 1967, $7,848,000; 1968, $7,848,000.

Mr. FLOOD. I think the record should show that we are very happy that our friend, Mr. Cardwell was recognized for his outstanding service just yesterday afternoon. As I understand it, he was presented with the Department's Distinguished Service Award. This is a mark of distinction by his Government and his Department, with which this committee certainly concurs.

Mr. CARDWEL. Thank you very much, sir.

Mr. FLOOD. Now we have Dr. Dorland Davis, who is the Director of the National Institute of Allergy and Infectious Diseases.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

We have a biographical sketch of the doctor which will be inserted in the record at this point.

(The document follows:)

Name: Dorland J. Davis, M.D.

Position: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Birthplace and date: Chicago, Illinois, July 2, 1911.

Education: B.S. (with highest honors), University of Illinois, 1933; M.D., Johns Hopkins University, 1937; Dr. P.H. (epidemiology) Johns Hopkins University, 1940; Certified by the American Board of Preventive Medicine and Public Health, 1949.

Experience: 1964 to present: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; 1956 to 1964: Associate Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; 1954 to 1956: Chief, Laboratory of Infectious Diseases, National Microbiological Institute (now National Institute of Allergy and Infectious Diseases), National Institutes of Health; 1944 to 1954: National Institute of Health, Division of Infectious Diseases; 1943: Duty in North Africa for the State Department and U.S. Army; 1939 to 1943: National Institute of Health, Division of Infectious Diseases (appointed May 27, 1939).

Association memberships: (1) Medical Society Membership—Fellow, American Association for the Advancement of Science; Fellow, American Public Health Association (member of the Governing Council); Fellow, American Academy of Microbiology; Fellow, American College of Preventive Medicine; Society of Experimental Biology and Medicine; American Association of Military Surgeons; American Association of Immunologists; American Society for Microbiology; American Epidemiological Society; American Society of Tropical Medicine and Hygiene; American Medical Association; Scientific and Educational Council, Allergy Foundation of America. (2) Other Memberships—World Health Organization Expert Committee on Influenza; World Health Organization Panel on Virus Diseases; U.S. Representative for the Eighth International Congresses on Tropical Medicine and Malaria; Board of Directors, Gorgas Memorial Institute of Tropical and Prevention Medicine, Inc.; 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 U.S., 1955; Phi Beta Kappa; Sigma Xi; Delta Omega; author and coauthor of many scientific papers, primarily on the results of epidemiological and etiological studies of infectious diseases, including trypanosomiasis, psittacosis, hepatitis, bacterial conjunctivists, and influenza.

Mr. FLOOD. Do you have a statement, Doctor?

Dr. DAVIS. Yes, I have, Mr. Flood.

Mr. FLOOD. Will you proceed.

GENERAL STATEMENT

Dr. DAVIS. One has only to compare today's newspaper and magazine articles about public health with those of 50 years ago to know that medical science has made progress against infectious diseases. Vaccines, the products of research, have practically wiped out such former scourges as diphtheria, whooping cough, tetanus, and poliomyelitis. And thanks to antibiotics, advances have also been made in the treatment of such diseases as tuberculosis, venereal disease, and bacterial pneumonia. In short, medical research has paid off in the field of infectious diseases.

TUBERCULOSIS

Mr. FLOOD. Tuberculosis?

Dr. DAVIS. Tuberculosis, yes. The death rate for tuberculosis has declined dramatically since 1900. Unfortunately, at the present time there seems to be a plateauing. The decline was due in large part to the

improved sanitary conditions, improved economic conditions, and better public health practice.

Mr. FLOOD. Has the incidence not increased lately?

Dr. DAVIS. In the center of cities where there are slum conditions, and poverty, there have been some increases in the death rate and in the incidence, but these are rather isolated.

Mr. FLOOD. We are having trouble in other parts of the world, are we not?

Dr. DAVIS. Tuberculosis is one of the most important diseases in the world. Even in tropical areas where we think of other diseases as being so important, we find when we look at morbidity statistics, and death certificates, that tuberculosis is extremely important. I am speaking such areas as Central America, South America, Africa, and India.

Dr. SHANNON. And Southeast Asia.

Dr. DAVIS. Southeast Asia.

DIMENSIONS OF THE INFECTIOUS DISEASE PROBLEM

Despite these advances, infectious diseases and related allergic and immunologic disorders are still one of the Nation's major public health problems. As a group, these conditions rank third as a cause of death, accounting for some 110,000 deaths a year. This number includes 10,000 children who die of respiratory infections in their first year of life.

Mr. FLOOD. Cystic fibrosis?

Dr. DAVIS. Yes, although deaths from cystic fibrosis are now projected later on in childhood rather than as they were some years ago in the first year of life.

It is due to the effective use of antibiotics in the management of cases of cystic fibrosis. When one remembers that each of these infant deaths represents a lost lifetime, the real loss amounts to more than 700,000 man-years of life annually.

But the toll does not stop there. The American people suffer more than a quarter of a billion episodes of acute infectious disease every year. And 17 million Americans suffer from allergies. The annual cost is staggering: 850 million days of restricted activity, 110 million lost workdays, 160 million lost schooldays, $1.5 billion in lost productivity, and upwards of $1 billion spent for medical treatment.

RESEARCH AND TRAINING

The programs of research and research training conducted and supported by the Institute are designed to relieve the American people of this enormous medical and economic burden.

The Institute's program, however, has a broader significance than is indicated by mere statistics. Research in microbiology and immunology nourishes the entire field of biomedicine and has an impact on the research programs of the other Institutes. Here are just two cases in point, one from the field of virology, the other from immunology.

First, animal studies continue to yield evidence that viruses may also be a cause of cancer and of such chronic conditions as degenera-

tive neurological disorders. The intensive study of viruses may hold the key to the eventual conquest of these diseases.

Second, the major barrier to successful kidney and other organ transplantation is presently a problem in immunology; namely, rejection of the transplanted organ due to the body's defensive immune response, which is triggered by any intruder, whether it be a life-saving transplant or a life-threatening microbe. Research in immunology holds the key to overcoming that barrier. It may also lead to ways of preventing some kinds of kidney disease, such as chronic glomerulonephritis.

The allergic and infectious diseases pose a great challenge to medical research scientists. Not only does the field encompass several hundred distinct diseases, but there are several thousand different agents—viruses, bacteria, fungi, parasites, richettsiae, and allergenic substances—that can afflict man. All these diseases and agents must be studied. Knowledge of their characteristics make possible improved prevention, diagnosis, and treatment, and contributes meaningfully to the general progress of man's understanding of life processes.

STRATEGY FOR ATTACK ON DISEASE

As was pointed out in a special report prepared recently for the President, due to practical limitations on resources, the Institute has established priorities in its research program, apart from the necessity to support a broad program of general research and research training. In the selection of priority areas, account is taken of three factors: (1) the public health impact of the disease problem, (2) the state of knowledge in the particular scientific field, and (3) available manpower and facilities.

The Institute's present strategy includes three forms of attack on disease.

The first, which spearheads the Institute attack, is the broad program of scientist-originated fundamental research being supported at medical centers throughout the Nation and conducted at the Institute's own outstanding intramural laboratories in Bethesda, Md., Hamilton, Mont., Atlanta, Ga., and the Panama Canal Zone. The second comprises uncontrolled, but planned, grant-supported or intramural special emphasis programs, which are aimed at uncovering new knowledge about selected disease problems. And the third consists of collaborative, goal-oriented, centrally managed, contract-financed nationally organized research and development programs, which are designed to translate new knowledge into products and techniques of immediate benefit to human beings.

PROGRAMS IN PARTNERSHIP WITH INDUSTRY

The Institute is presently conducting four nationally organized programs in partnership with industry, university research centers, and other Institutes of the NIH. The respiratory virus vaccine development program is developing and evaluating vaccines against acute viral respiratory infections, the cause of more than half of all illness in the United States. The transplantation immunology program is developing materials and methods for overcoming the immunologic barrier to successful organ transplantation. The rubella, or German

measles, vaccine development program is developing and evaluating vaccines against a virus that kills and cripples unborn children. And the research reference reagents program produces, tests, and distributes to research scientists uniform samples of viruses and virologic materials useful in studies of many infectious diseases.

SPECIAL EMPHASIS PROGRAMS

The special emphasis programs are designed to focus the attention of scientists on important, difficult, or neglected problems; to support the necessary fundamental research by grants or conduct it at the Institute's own laboratories; and to promote the exchange of information among scientists so that gaps in knowledge will be highlighted and opportunities for research will be recognized. The following diseases are those on which attention is now being focused; tuberculosis, which still strikes 50,000 Americans every year; emphysema, a crippling chronic lung disorder that ranks second only to heart disease as a disabler of workingmen over 45; infectious hepatitis, which afflicts upward of 40,000 children and adults a year; chronic degenerative disorders, such as multiple sclerosis, whose causes are still a mystery; drug-resistant parasitic and bacterial diseases, such as falciparum malaria and meningococcal and staphylococcal infections; allergies, such as hay fever, asthma, and food and drug hypersensitivities, and the less familiar autoimmune disorders, in which the body seems to turn on some of its own cells as if they were a harmful invader; and such virus diseases as influenza and the common cold, which might be effectively controlled through treatment with chemical or biological compounds rather than by means of vaccines.

Mr. FLOOD. The common cold might be?

Dr. DAVIS. Yes, sir. We hope that eventually we will have antiviral agents not only for the common cold but for other respiratory infections that are due to viruses. The antiviral substances program or the viral chemotherapy is one of our major concerns in the Institute. In fact, we have a large grant program amounting to over $4 millian which is supporting investigations at a fundamental level on the nature of viruses and the effect of various drugs and chemicals upon the constitution of the viruses. We hope that this will lead us to practical drugs with which to control virus infections such as the common cold.

Mr. FLOOD. Drugs or a vaccine?

Dr. DAVIS. Drugs for treatment or prevention of the disease after exposure. There are now two which are quite effective. One is iodooxyuridine, a compound which has been used in the last 4 or 5 years for herpetic keratitis, which is an eye infection. Another one seems to be effective against smallpox, provided it is given shortly before the disease occurs. This is thiosemicarbozone. These are drugs that have been used clinically.

Mr. FLOOD. I see you have a special report on respiratory vaccine development. We will place that in the record at this point.

(The report follows:)

Special Report: Respiratory Vaccine Development

THE ACUTE RESPIRATORY DISEASES

Every year 250 million *reported* acute respiratory ailments plague the people of this country. This figure grossly understates the actual incidence of these diseases, since Americans annually suffer an estimated 500 million colds. Acute respiratory ailments account for about half of all illness in the Nation and include everything from mild colds to incapacitating febrile illnesses and pneumonia.

The death toll from acute respiratory diseases is high. It averages about 70,000 annually and accounts for about 70 percent of the deaths from all infectious diseases in the country. About 10,000 infants die each year from these diseases. Days lost from work and reduced productivity due to acute respiratory diseases cost industry $3 billion a year. The added cost of medical treatment (more than $1 billion), the time required of physicians to care for patients (12 million hours), and the school days lost by children (108 million) underscore the enormity of the problem.

APPROACHES TO SOLVING THE PROBLEM

An infectious disease can be attacked by eliminating the responsible organism or its carrier, thus preventing its spread; by immunizing the population with vaccines; or by treating the disease with effective drugs after it has developed.

Every human at one time or another is invaded by the organisms that cause acute respiratory infections, is host to them while they multiply, and passes them on to his fellow man. There is no known intermediate animal host and the organisms are so prevalent that this chain of contact-reproduction-spread can be broken only by preventing the disease.

While antiviral substances—that is, chemicals for treating viral diseases as antibiotics and sulfas are used against bacterial diseases—would be ideal, these drugs are still in early stages of research.

Vaccines to prevent the development of viral (and some non-viral) respiratory diseases are presently the most promising means for their control.

Although a large number of viruses (up to 150) can cause acute respiratory diseases, a relative few account for a high proportion of the total illness. The respiratory syncytial virus and parainfluenza viruses 1, 2, and 3 cause about 30 percent of all serious respiratory illness in children. Adenovirus-4 is a primary cause of severe acute respiratory disease in military trainees. *Mycoplasma pneumoniae*, though not a virus, causes a large proportion of acute respiratory disease in school-aged children and young adults and is believed to be amenable to control by vaccination. The rhinoviruses, which cause the common cold, comprise a large group of organisms, complicating the task of developing vaccines against them. However, the well-known frequency of the minor but troublesome illnesses they cause makes a major effort worthwhile.

These are the groups the Institute has chosen as the initial candidates for vaccine development. It is thought that much of the respiratory illness in the country will have been dealt with if the search for these vaccines is successful. Other organisms causing acute respiratory infections will then be considered for vaccine development.

THE NIAID COLLABORATIVE PROGRAM

The Institute's Collaborative Research Program is designed to translate basic research knowledge into specific products for preventing and treating infectious diseases. The purpose of the program is to bring the benefits of research to the American people as quickly as possible.

Recent scientific and methodological advances have made it possible to produce vaccines that could not have been made a few years ago. Many of these advances were made in the Institute's intramural laboratories where a number of organisms responsible for acute respiratory diseases were first isolated and where methods for handling these agents have been developed.

But converting these advances into vaccines will not be easy, since a wide variety of approaches are necessary to bring the many diverse organisms under control in a relatively short period of time. The Institute's collaborative Respiratory Vaccine Development Program was set up in 1962 with this goal in mind. It was given the task of making and testing prototype respiratory vaccines through collaboration with contract-financed university and industry research groups.

THE PROGRESS OF THE RESPIRATORY VACCINE DEVELOPMENT PROGRAM

The Respiratory Vaccine Development Program is now nearly 5 years old. During this time, an effective partnership had been created between universities, medical centers, the pharmaceutical and allied industries, and the Government, and a smoothly working administrative system has been devised. The Vaccine Development Branch of the Institute's Collaborative Research Program plans, directs, and coordinates the complex program, with the advice and counsel of an advisory committee. The Institute's intramural scientists act as project officers, constantly monitoring the work being done by university and industrial contractors; at the same time, these Institute scientists continue to contribute original research findings to the Program. Through the intensive efforts of this closely coordinated team, several very promising experimental respiratory vaccines have so far been developed.

Although this ambitious program still has far to go, and although disappointments as well as successes have been encountered, a number of significant advances have already been made on the long road toward the ultimate control of acute respiratory diseases.

AN EFFECTIVE ORAL ADENOVIRUS-4 VACCINE

Early in World War II, the military became concerned about acute respiratory infections which immobilized large numbers of soldiers in training camps. These acute febrile illnesses, 10 percent of which were pneumonia, and many of which required hospitalization, were a major source of lost manpower and money. An epidemic season at a single camp cost the Army as much as $10 million.

Much of this acute respiratory disease was traced to the adenoviruses, and adenovirus type 4 was pinpointed as the major cause.

Under the Respiratory Vaccine Development Program, an oral adenovirus–4 vaccine has been developed. This vaccine, which was first conceived and produced in the Institute's intramural laboratories, represents a new concept in vaccines. Originally it consisted of a coated, delayed-release capsule which did not break up until it reached the intestinal tract. There the released live virus caused a symptom-free, noncontagious infection which triggered the production of antibodies. This capsule has recently been improved upon by a smaller, pressed tablet which is easier to swallow and which accomplishes the same results.

After the adenovirus–4 vaccine proved successful in volunteer studies, it was field tested in about 300 recruits at a Marine training camp. This first field trial was 100 percent successful. The trials were then enlarged. Latest reports from large-scale clinical trials at military bases in several parts of the country show that the vaccine produces excellent results. It has been effective in preventing acute respiratory disease, in interrupting epidemics in progress, and in conferring a certain degree of "herd immunity" on those who remain unvaccinated.

A PROMISING PARAINFLUENZA VACCINE

Parainfluenza viruses 1, 2, and 3 cause a fifth of the acute respiratory diseases serious enough to hospitalize infants and small children. These viruses, which were first isolated in the Institute's intramural laboratories, spread rapidly from person to person and mainly cause illness in children in the form of croup, bronchitis, and pneumonia.

Separate injectible killed vaccines against each of these virus types were among the earliest developed by the Respiratory Vaccine Development Program. They were first tested for safety in adult volunteers. Then they were given to small children and found to be 90 to 100 percent effective in stimulating a significant rise in protective antibody. Recently the three separate vaccines were combined into a trivalent one, which is now being tested against the natural disease. More than 3,000 children are presently participating in these studies. If the

vaccine continues to show success, the studies will be expanded to include larger groups.

The need to raise antibody levels quickly for protection against illness when the disease is prevalent has led to efforts to administer parainfluenza vaccine intranasally. This work is still in a very early stage.

A DISAPPOINTING MYCOPLASMA PNEUMONIAE VACCINE

Mycoplasma pneumoniae is an organism which shares the features of both bacteria and viruses. First known as the Eaton agent and believed to be a virus, it was identified as a mycoplasma by a scientist in the Institute's intramural laboratories. This organism is a major cause of primary atypical pneumonia in children and young adults. In epidemic years it accounts for 10 percent of all respiratory illness in small children, while in the age group from 10 to 20 years, it causes up to 30 percent of all pneumonia.

The Vaccine Development Program prepared several killed vaccines against *M. pneumoniae*, gradually improving them, increasing their concentration, and lessening their potential to produce allergic reactions. The latest vaccine produced excellent protection against infection in rabbits and hamsters. It was also promising in small-scale studies in humans. However, when large-scale field trials were conducted at military training camps, the vaccine was found to be relatively ineffective. Scientists agree that the antibody produced by *M. pneumoniae* is capable of protecting against infection, but that the present vaccine does not produce enough antibody in man to afford protection.

In the meantime, other studies supported by the Vaccine Development Program have shown that school-aged children are the main group affected by *M. pneumoniae* and are largely responsible for its spread. It has also been found that the organism has a long period of incubation (averaging about 3 weeks), which can mask its role in causing infection. Because of this long incubation period, an intranasally administered vaccine might have the advantage of raising antibody titers to protective levels quickly. Studies are being conducted on this method of administration.

The Vaccine Development Program is now directing its efforts toward modifying the *M. pneumoniae* vaccine so that it will stimulate the production of adequate protective antibody.

AN ELUSIVE RESPIRATORY SYNCYTIAL VACCINE

The respiratory syncytial virus, first isolated in the Institute's intramural laboratories, kills an estimated 5,000 infants a year. This is half of all the babies who die from acute respiratory diseases. Virtually no one is immune to infection with this virus, but infants under 6 months present a particularly difficult problem. Because of the high mortality rate associated with this disease, it is imperative that an effective vaccine be developed against it.

Developing the respiratory syncytial vaccine will not be easy, however. A major obstacle is the difficulty in conferring good immunity. Even a severe infection with the respiratory syncytial virus does not leave the patient immune. Any of several problems may be involved: The virus may be a poor stimulus to antibody production, its antigen (that part of the virus which triggers antibody production) may not be sufficiently concentrated, or there may be a defect in the antibody the human body produces against it. Further problems in producing a vaccine are that the virus is difficult to grow in quantity and the vaccine produced does not keep well in storage.

Very small trials are now in progress in children and in volunteers with a respiratory syncytial vaccine developed under the Vaccine Development Program. But so far it has given little protection against the infection.

As with parainfluenza and *M. pneumoniae*, efforts will be made to administer a respiratory syncytial vaccine intranasally.

Further studies are needed on the respiratory syncytial virus, its antigens, and the antibodies resulting from infection with the organism. A major effort will be exerted by the Vaccine Development Program in the hope of producing an effective vaccine against the virus within the next 5 years.

A START TOWARD RHINOVIRUS VACCINES

The rhinoviruses are primarily responsible for causing the common cold. Although most of these illnesses are not serious, they do run up formidable medical bills and cause absenteeism, lowered productivity, and poor performance in fac-

tory, office, and classroom. In addition, they lower their victims' resistance to other, more virulent infections.

Over the past few years, research scientists have isolated a large number of rhinoviruses. Following a program of testing and identifying distinct types, most of which was sponsored by the Vaccine Development Program, an international nomenclature for rhinoviruses was ratified by the International Microbiology Nomenclature Committee in July 1966. This system includes 55 rhinovirus prototypes against which viruses isolated in the future can be compared and classified.

Vaccine development efforts have progressed to a point where several candidate rhinovirus vaccines are expected to be available for clinical trials in the near future.

A SUMMARY OF ACCOMPLISHMENTS

In its first 5 years of work, the Respiratory Vaccine Development Program has had several successes. An oral adenovirus-4 vaccine has proved highly effective and will soon be tried in over half a million people. A trivalent parainfluenza vaccine has shown early promise. Vaccines against some rhinoviruses are almost ready for testing. Unfortunately, after an encouraging start, results in large trials with an *M. pneumoniae* vaccine have been disappointing. The vaccine will be modified to give better protection before trials are continued. Difficulties are still being presented by the respiratory syncytial virus, hampering efforts to make an effective vaccine against this organism.

A LOOK TO THE FUTURE

In the future, great emphasis will be placed on expanding the field trials of the adenovirus-4 and the trivalent parainfluenza vaccines. Rhinovirus vaccines will be tested as soon as they become available. Strenuous efforts will be made to improve the *M. pneumoniae* vaccine and to perfect a vaccine against the respiratory syncytial virus. Subunit vaccines consisting of parts of a virus will be developed where they are needed to promote better protection or to eliminate undesirable effects caused by the whole virus. Some attempts will be made to develop oral vaccines for respiratory agents other than adenovirus-4. And because nasal antibody is believed to give the best protection against respiratory diseases, some efforts will be made to administer vaccines intranasally in the hope of locally stimulating the production of nasal antibody.

ROLE OF FUNDAMENTAL RESEARCH

Dr. DAVIS. I cannot stress too much the essential role of fundamental research, conceived and conducted by the Institute's scientists and grantees, in the attack on allergic and infectious diseases. It is such research, which explores new ideas and new techniques, that makes all medical advances possible. Every technique, every drug, and every vaccine used today to prevent, treat, or relieve allergies and infectious diseases had its beginning in the laboratory of some fundamental research scientist. The same is true of every other field of medical practice. That is why the Nobel Prize in medicine and physiology invariably goes to someone who has worked on the frontiers of virology, molecular biology, genetics, cell physiology, biochemistry and immunology—where many of our own scientists and grantees are working today. And speaking of the Nobel Prize, I think this committee would be interested in knowing that in the past 13 years, fundamental research scientists (microbiologists, immunologists, geneticists) who were being supported by grants from this Institute have won five Nobel Prizes in recognition of their outstanding achievements and their contributions to the advancement of human knowledge and the relief of human suffering.

Time does not permit me to discuss all the research advances reported by the Institute's scientists, grantees, and contractors in 1966.

Many of these are described extensively, however, in the special reports submitted earlier to the committee, including our detailed highlights report. I shall briefly describe here, therefore, just two representative and highly encouraging accomplishments of the past year, one from the broad field of immunology, the other from virology.

TISSUE TRANSPLANTATION PROGRAM

The first encouraging advance came in our tissue transplantation program. The short-term goal of that program is a battery of tissue-typing tests for matching donors and recipients of organ transplants (in much the same way that blood donors and recipients are matched today) and thereby reducing the danger of organ rejection due to tissue incompatibility. Reports by scientists engaged in the program encourage me to say that not only have prototype tissue-typing tests been developed but they appear to work. One investigator has already matched unrelated prospective donors and recipients of kidney transplants, and the success rate of transplants between these unrelated but matched persons has approached that of transplants between relatives.

Mr. FLOOD. Is that organs or skin?

Dr. DAVIS. These refer to kidneys.

Mr. FLOOD. All right.

VACCINE DEVELOPMENT PROGRAM

Dr. DAVIS. Last year I reported to this committee on the first successful field trial of an oral vaccine against adenovirus type 4, the major cause of outbreaks of severe acute respiratory disease at military training camps. That vaccine was the first payoff of our nationally organized vaccine development program. It is a tribute to the fundamental research scientists in our own intramural laboratories who conceived it and to the scientist administrators in our collaborative program who directed its development and evaluation.

This year I am pleased to report another important advance. Experimental vaccines against three types of parainfluenza viruses, major causes of croup and bronchopneumonia in young children, showed promise in early tests at Children's Hospital of the District of Columbia. The vaccines, which were developed in our own intramural laboratories, were found to be completely safe and 90 to 100 percent effective in stimulating a significant rise in the level of protective antibody in youngsters. The three vaccines have been combined into a single preparation which is now being clinically evaluated at Children's Hospital and the Universities of California and Colorado.

EMPHASIS ON VIRUSES

It is not by accident—nor do I believe it has escaped the attention of the committee—that a good part of this statement and an even larger part of our special reports deal with the subject of viruses and virus diseases. This emphasis simply reflects the paramount role of virology in the Institute's program.

Medical science has much to learn about viruses and the diseases they cause. For example, many viruses, such as those believed to cause infectious hepatitis and epidemic diarrhea, still cannot be isolated

and identified due to a lack of proper techniques and adequate facilities. But much ground has been gained.

We know that most viruses are so small that they can be seen only with the aid of an electron microscope. Pictures taken through such an instrument show a variety of forms: cubes, rods, spheres, spirals, and some even more complex. Essentially a virus consists of a protein shell arranged around long, coiled strands of nucleic acids, either DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). These coiled molecules, shaped like a long ladder twisted in a continuous spiral, carry the complete coded genetic instructions for reproduction of the virus.

One of the most important findings of virologists is that infection by a virus does not necessarily follow a single course—namely, swift virus reproduction and the development of a specific infectious disease, such as influenza, with resulting cell destruction. That is only one of several possible courses.

In another, reproduction may be slow, without the development of clinical disease. Or the virus may become a latent border in the cell for an indefinite period. Should certain biochemical changes take place in the host cell, however, the slumbering virus could change into a virulent form. That is what some investigators suspect happens in chronic degenerative neurological disorders.

Still another possibility is that the virus genetic material (DNA or RNA) may take over control of the machinery of the host cell. Instead of reproducing itself, causing an acute infection, and killing the cell, the virus may transform the cell. The result is cell growth gone wild—or cancer.

To carry on the research attack against viruses and the many other microbes and allergens that make man ill, cripple him, and cut short his life, the 1968 request for the National Institute of Allergy and Infectious Diseases is $94,422,000, including $500,000 for the Gorgas Memorial Laboratory. A comparable operating level for 1967 is $87,-244,000. The 1968 funds requested provide a net increase of $3,930,000 for research grants; $567,000 for fellowships; $148,000 for training grants; $1,258,000 for laboratory and clinical research; $1,071,000 for collaborative research and development; $67,000 for biometry, epidemiology, and field studies; $124,000 for review and approval of grants, and $13,000 for program direction.

Mr. FLOOD. This is a dissertation on viral diseases; what about bacteria?

Dr. SHANNON. I think if you pursue one of the questions which was raised earlier, namely, the work being done in the field of immunizing agents for tuberculosis, I think this could well bring out some of the activities of the bacteria-oriented program.

Mr. FLOOD. He ought to discuss one of them.

Dr. SHANNON. The other one he has responsibility for is the conduct of a cholera research laboratory, financed largely by funds transferred to us by the State Department, operated for SEATO nations. This is undertaken in Dacca in East Pakistan. This is a bacterial disease of great consequence to the Southeast Asian nations.

Mr. FLOOD. I thought you were going to say something about development of resistance to drugs. Aren't they taking the drugs as a sort of a dessert?

STAPHYLOCOCCAL INFECTIONS

Dr. SHANNON. This is particularly true of staphylococcal infections, not uncommon in hospital situations.

During the early days of the antibiotics, they were so effective against common infections of this sort that, indeed, they did modify basic techniques. When it turned out that staphylococcal infections in postoperative situations were——

Mr. FLOOD. It got pretty bad for a while, did it not?

Dr. SHANNON. They were almost as high as they were before any of these agents became available. One went back to the less specific, more arduous control of the bacteria which had been the only method of control that existed prior to the availability of the new drugs. My understanding is that these infections still constitute a very serious hazard in a wide variety of hospital procedures.

Dr. DAVIS. This is true. There are two bacteria which we are particularly concerned about. One is the staphylococcus in hospital situations. In addition to the measures which were indicated awhile ago, we have more careful monitoring of the nurses and doctors who work in the hospitals as carriers of staphylococcus.

Mr. FLOOD. More careful monitoring?

Dr. DAVIS. It has been found that attendants of patients, including nurses and doctors, frequently carry staphylococcal bacteria in their respirator tracts. Very frequently these are drug resistant. They may infect patients. So that in most hospitals now if there is a problem, the attendants are cultured to determine whether or not there are any of these drug-resistant bacteria in their respiratory tracts. If they are found, the nurses may be transferred to another situation. In other words, they are looking for the source of this infection.

MENINGOCOCCUS

There is another bacteria which is causing a lot of trouble and that is the meningococcus, the cause of spinal meningitis.

For instance, we know that something like 20 percent of the men who come to recruit camps carry drug-resistant meningococci in their respiratory tract.

Mr. FLOOD. We have had very little problem at the cantonments with meningitis lately, have we not?

Dr. DAVIS. That is true. There has been very careful control. Many of them have been given prophylaxis.

Mr. FLOOD. The last outbreak was in California?

Dr. DAVIS. Fort Ord, yes; they had numerous cases. That was due to drug-resistant organisms.

TUBERCULOSIS VACCINE

I might, if I may, mention the tuberculosis vaccine work which has been going on for some years.

Mr. FLOOD. You have not gone very far on the vaccine for tuberculosis have you?

Dr. DAVIS. The vaccine that we have worked on showed great promise in the experimental situation.

Mr. FLOOD. How long ago has that been, 3 or 4 years?

Dr. DAVIS. Yes.

Mr. FLOOD. What happened? Nothing.

Dr. DAVIS. When we attempted to transfer the results in mice and evaluate it in monkeys, as happens so frequently, we did not get good results. So we are having to go back and find out more fundamental information. The principle is right. We are using a cell wall fraction of the organism. It has good expectation of producing protection without the sensitizing factor which is the big trouble with BCG, for instance.

Mr. FLOOD. So you read the Reader's Digest, too, do you?

Dr. DAVIS. Yes.

Dr. SHANNON. What is the significance?

Mr. FLOOD. Well, there is that famous Reader's Digest story about BCG against tuberculosis. Do you remember that article?

Dr. SHANNON. In a country like this, the highest attack rate of tuberculosis is among those individuals who show a sensitivity to BCG which precludes the use of BCG as a preventive measure. In other words, they have some minimal infection already existing at the time they are tested. BCG does not produce the simple, nonsensitizing type of immunity one wishes.

Mr. FLOOD. A few years ago we thought you had it about licked. This morning you do not.

Dr. SHANNON. I did not think we had it licked a few years ago. I thought we had an animal model system out of which might come a vaccine but, as so frequently happens when you bring it to trial, it had to go back to the bench. This is precisely where it is, back at the bench. This is a problem of great consequence not only to ourselves but of much greater consequence to Southeast Asia where we are committed to a joint program with Japan, funded at quite a low level in which this is one of the most important areas for research emphasis. If they come up with a usable antigen, in the form of a practical vaccine, in a period of time as short as 5 years, I think they will have accomplished something.

Mr. FLOOD. How are the Japanese? Are they pretty good in this kind of thing?

Dr. SHANNON. I think the Japanese are very good scientists. The problem is they are undersupported in relation to their capability. They share with the Russians, as contrasted to our own scientific society, a lesser strength in depth in the various fields but they are good people, just as good as our good people. It is just that they have fewer.

Mr. FLOOD. When they are good, they are really good; is that it?

Dr. SHANNON. Yes, sir.

SUMMARY OF BUDGET REQUEST FOR ALLERGY AND INFECTIOUS DISEASES

Mr. FLOOD. The adjusted appropriation for 1967 is $87,408,000. Your request for 1968 is $94,422,000. That is an increase of $7,014,000. Now, that makes you about average. That puts you up about 8 percent.

Dr. DAVIS. Yes.

UNOBLIGATED BALANCE IN RESERVE FOR SAVINGS

Mr. FLOOD. You must be very important; in 1967 they clipped you only $164,000 for this "Unobligated balance, reserve."

Dr. DAVIS. Yes.

Mr. FLOOD. Why such a light touch on you?

Dr. DAVIS. Mr. Flood, our program for several years now has been at a disadvantage with a large backlog in the grants programs. We have been able to pay only about 70 percent of the approved grants.

RESEARCH GRANTS

Mr. FLOOD. Yes, that is what I thought. Now, over half of this increase, $3,930,000, is for research grants. You would be able to support 1,483 projects in 1968. That is an increase of 103. To what research are you giving priority?

MICROBIAL CAUSES OF CHRONIC AND DEGENERATIVE DISEASES

Dr. DAVIS. We are going to put these funds into about four areas. One is the microbial causes of chronic and degenerative diseases, including emphysema?

Mr. FLOOD. Yes. I come from the coalfields. We know a good deal about it because we have a similar problem that we call asthma. This is something else, I know.

Dr. DAVIS. There is a distinction between asthma and emphysema.

Mr. FLOOD. Yes. Both are very unpleasant.

Dr. DAVIS. Yes.

DRUG RESISTANCE

Another we are emphasizing is one we mentioned a little while ago, the study of drug resistance. Just why is it these bacteria, staphylococcal, meningococcal, including tuberculosis, became resistant to the commonly used therapeutic drugs? We are also stressing antiviral substances, chemotherapy and chemoprophylaxis for virus infections.

TISSUE TRANSPLANTATION

Another one of our main areas is tissue transplantation immunology, which develops fundamental information about the immunologic reaction to transplanted tissues and ways of preventing it.

Mr. FLOOD. By tissue, do you mean organs or just tissue?

Dr. DAVIS. Organs, but it is a general phenomenon so we use a general term in discussing it. It could apply to any one of the organs. As you know, the kidney is the organ that has had the most attention. Actually, in the last few years there have been 1,200 transplants of kidneys in the world. These are going on rapidly in many different centers in this country and in Europe particularly.

Mr. FLOOD. In the same family or from strangers?

Dr. DAVIS. The donor may or may not be in the same family. The results are better if the donor is a brother or sister. In that experience there has been about a 75-percent survival rate over 2 years.

Mr. FLOOD. What about age brackets?

Dr. DAVIS. They usually are not done in the older age groups. Usually middle age is the age of choice. To my knowledge, there is no difference in the survival rate between the different ages. These are almost primarily done in middle-age adults.

Dr. SHANNON. Mr. Chairman, while Dr. Davis mentioned it, I do not think he emphasized enough the major advance in this area, the typing of tissues; that is, the identification of the antigens in the body that cause a reaction to the tissue transplanted. If one can type the antigens suitably, it turns out that not a very large number of antibodies are produced and it is possible to obtain in nonrelated individuals almost as high a proportion of takes as one heretofore has gotten with identical twins.

Mr. FLOOD. You are not going to stop with kidneys?

Dr. SHANNON. No, sir, but that is a convenient organ to emphasize because it is possible to follow the functioning of that organ precisely.

Mr. FLOOD. Don't you want to transplant everything, if you could ultimately?

Mr. SHANNON. Quite frankly, no, sir. I do not want to live to be 150, or some such thing as that.

These techniques were pioneered in Europe, rather than in the United States. The most active laboratory in this country is the laboratory of Dr. Bernard Amos, at Duke University. He is working on a proposal, at such time as it is felt that the typing systems are sufficiently well elaborated, to type large numbers of people with chronic kidney disease in anticipation of later need for transplantation of kidneys. He has pointed out that the Veterans' Administration system is peculiarly suited for that massive type of recording of data. It will probably be in medical systems of that general type that this will first find very broad application. If tissue typing does turn out to be somewhat more complex but nonetheless as precise as blood typing is at the present time, then the possibility of transplantation as an everyday occurrence will become a reality. Now, I would point out, on the other hand—going back to Dr. Whedon's testimony—that this in no way minimizes the need for renal dialysis. Although renal dialysis, if we have the ability to transplant, will no longer be the permanent tool for treating the disease, it becomes an essential part of the process that prepares the patient for the transplantation process. To give you the total picture, I would point out that one of the problems of the transplanted kidney is that the major cause of chronic renal insufficiency—leading to the need to transplant or leading to the need to dialyze—is the diseased condition called chronic glomerulonephritis, which causes progressive deterioration. The unfortunate thing is that when one transplants a kidney—even though one gets a viable organ in a substantial percentage of cases—the diseased condition in the body——

Mr. FLOOD. Of course, we have two. We are lucky in this case.

Dr. SHANNON. Unfortunately, chronic renal insufficiency of this type attacks both organs simultaneously. The problem here is that the new kidney that is transplanted has a tendency to acquire the same disease that destroyed the old one. The experimental approaches that are now available come from a discovery, during the past year, that it is possible to study this disease in an animal model. This information comes from Australia where hybrid mice have been shown

to have a disease indistinguishable from this. So, for the first time, there is an animal model system to study the disease in a more definitive fashion. You will recall that one of the points I made yesterday was that until one has an animal model system it is quite frequently impossible to do definitive work on very complex diseases. I believe that most of the people who are deeply concerned with chronic renal insufficiency look forward to a definition of precisely what this animal model system can do in elucidating what is a complex and a mysterious ailment. When you talk about chronic renal disease, you talk about the problems of hemodialysis, you talk about problems that relate to transplantation, your talk about problems of dietary control that minimize the need for dialysis or that compensate for the inadequacy of the biologic system, and then, finally, one has to consider the role that can be played by these new animal model systems in the elucidation of the disease.

I have spent some time pointing this out for two reasons: in part, because I suspect that this problem will be in the news today or tomorrow. It is summarized in some detail in the journal called Medical World News which I mentioned yesterday. And, in part, because the disease is sufficiently complicated and appears in the programs of a sufficient number of our Institutes that we have found it necessary to set up a group of our own scientists who cross Institute boundaries in their consideration of the total problem and the relative role played by these various approaches in the ultimate resolution of the problem. Increasingly, we are finding that serious problems of this sort make it impossible to contain them within a single Institute. We must cut across the barriers between them so that several Institutes can approach the problem.

FELLOWSHIPS AND TRAINING GRANTS

Mr. FLOOD. You have a small increase of 17 in the fellowships that you estimate you will be able to finance. Now, when you get into training grants—this is something we are very interested in—you have eight fewer continuations and three fewer new ones, for a total of 11 fewer grants. Why would that be? Man after man comes in here and says "We need this. We have to train these people." Now, you cut down 11 in an area like this. Why?

Dr. DAVIS. Well, Mr. Flood, in a time of restricted budgets we are not able to finance all of our requests for the support of ongoing research. So, for the present, it just seems to be more expedient to put our investment into supporting those scientists who are ready to go.

Mr. FLOOD. Who are on the job?

Dr. DAVIS. Who are on the job for the moment?

Mr. FLOOD. You learn your lesson well. That is the classical answer.

Dr. DAVIS. Yes.

DIRECT OPERATIONS

Mr. FLOOD. Now, for direct operations you have an increase of about $2.5 million and 13 positions. This seems to be a pattern. Every institute has an increase for direct operation regardless of what is being done about grants. You have a real increase for your direct operations.

Dr. DAVIS. Yes. We have a real increase and this permits us to emphasize some of the newer areas, areas which are expanding and ongoing, such as the study of virus etiology of chronic degenerative diseases, going on at the Rocky Mountain Laboratory. We also pursue studies in our laboratories here in Bethesda on respiratory viruses, including some of those that I mentioned, and a new group of bacteria-like organisms called the mycoplasma which we now have learned cause a large proportion of pneumonia in young adults.

PNEUMONIA

Mr. FLOOD. Why is there this flareup in pneumonia? It was passé for a while. Nobody had it. Now people are getting pneumonia. Why?

Dr. DAVIS. Following the introduction of the antibiotics, penicillin, and sulfapyridiene, the death rate for pneumonia decreased very markedly and the incidence decreased also. The actual death rate has now stabilized at about 20 percent. About 20 percent die usually within the first few days due to an overwhelming infection. I think one of the reasons, probably two reasons——

Mr. FLOOD. People are having pneumonia now. They did not have it for years.

Dr. DAVIS. I think one of the reasons is that our methods of diagnosis are probably becoming more acute. So a person might have what one would call a severe grippe which can now be diagnosed as pneumonia.

Mr. FLOOD. Grippe? I have not heard of that in 20 years.

Dr. DAVIS. Another thing, Mr. Flood, is that a larger proportion of our population is in the older age group. Pneumonia particularly attacks the older age groups. So it is becoming more noticeable now.

Dr. SHANNON. I would like to comment on your statement, sir. I mean the statement that you thought it was passé. I must confess that I was unaware of the figures when I selected pneumonia as one of two conditions for which to examine the effect on the cost of medical care of changing technology in the handling of diseases. One I took was syphilis and the other was pneumonia because, when I was a young intern in the hospital, the conventional stay in the hospital with pneumonia was about 14 to 20 days with a high mortality rate.

Mr. FLOOD. Of course, when you were an intern you stayed in the hospital 14 days for anything.

Dr. SHANNON. Yes, but this was accompanied by a high degree of complications, lung abscess, empyema and the like. At the present time, pneumococcus pneumonia in the young adult is usually treated by a physician in the home. He never sees the hospital and therefore one does not see, on the record, the benefits. I asked for a study to be made of the dollar cost of pneumonia in our society today and the other statistics associated with it. The answer I got was much like what Dr. Davis has just told you. It is believed, at the present time, that the answer to this problem is not one of further drug therapy, although this may help as the drugs available are modified. What actually has to be done is to go back and study the types that are now heavily involved in this high mortality—only about three or four of the 20-odd pneumococcus types. One should go back to 1933, 1934, and 1935—the days before sulfonamides became available—and resurrect what

was then a highly specific antigenic agent, in the form of a complex carbohydrate, that produced what appeared at that time to be a solid immunity. The answer to pneumonia, in the future, may have to be the addition of this type of immunizing agent to the array of immunizing agents that are now used. Hopefully, this will confer the type of permanent immunity we think is necessary.

Mr. FLOOD. What worries me is these things flare up. We got rid of smallpox, we are getting rid of polio, we are about to get rid of measles and all these things. But it seems if you are not looking they will jump right back at you; is that right?

Dr. SHANNON. Well, I was quite shocked at this. It is not a field in which I have particular competence but I was quite surprised. I think it is an important illustration of the fact, to use your words, that you must not forget your old friends. This type of analysis might well be placed in the record as an example of the false confidence we get when we appear to conquer a disease only to find out 10 or 15 years later we indeed have not. It might be interesting.

Mr. FLOOD. I think so.

Going back to the discussion of organ transplants, all you have talked about is the kidney.

ORGAN TRANSPLANTATION

Mr. DAVIS. This is the only organ which has been successfully transplanted in man. In dogs and in other animals experimented work has proved the feasibility of transplanting lungs or even a liver.

Mr. FLOOD. Even a liver?

Dr. DAVIS. Even a liver.

Mr. FLOOD. Is that very difficult?

Dr. SHANNON. It is very complex.

Dr. DAVIS. But this is only in the experimental stage. For some time there has been transplantation of bone marrow which is a tissue transplantation. Bone marrow is taken from a healthy donor and injected into the blood stream of a person who has an anemia which might be natural or might be a result of some drug therapy. This transplantation has proved quite successful. The work with skin has been tried for many years but the skin is the most difficult of all the organs to transplant. It is most likely to be rejected.

Mr. FLOOD. You mean from a stranger?

Dr. DAVIS. Yes. The only way we can transplant skin is through what we call the autograft from one part of the body to another. It is hoped that if we can solve this problem of tissue antigens and develop techniques for matching them that perhaps we will be able to successfully select the right skin donors.

Dr. SHANNON. We are not ready to go into the spare parts business yet.

RUBELLA VACCINE

Mr. FLOOD. Dr. Shannon told us and the Surgeon General told us something about rubella vaccine developments. They both said that when you got here you would say something about it.

Dr. DAVIS. Our institute has an active program for the practical development of a rubella vaccine.

Mr. FLOOD. I know that.

Dr. DAVIS. We have been very active in this during this past year. You will recall that just about a year ago Dr. Parkman and Dr. Myer announced that they had an attenuated strain which opened up the possibility of using a live attenuated strain of vaccine. With this advance, which is a very great advance——

Mr. FLOOD. This is April 1967. When are you going to get a breakthrough on this one? You have the other one licked.

Dr. DAVIS. We have been trying among ourselves to estimate when we would have an effective vaccine.

Mr. FLOOD. What is an educated guess on rubella?

Dr. DAVIS. I think we will have it before the next epidemic which we expect in about 3 years. The situation is that we do have an attenuated live strain which in very small studies does prevent rubella in children but there are certain difficulties that have yet to be worked out.

Mr. FLOOD. We will place your special report in the record.

(The report follows:)

SPECIAL REPORT: THE NIH ATTACK ON RUBELLA

One of the most tragic and disastrous epidemics to hit the United States in modern times was the rubella (German measles) epidemic of 1964–65. With reports still coming in on the havoc the epidemic left in its wake, it is conservatively estimated that the catastrophe resulted in upwards of 30,000 abnormal pregnancies. In addition to thousands of fetal and newborn deaths, some 20,000 infants were born crippled with such defects as cataracts, deafness, mental retardation, and heart disease.

THREAT TO THE UNBORN

Rubella is a common virus disease. In children it usually causes a mild illness. Often a slight headache, fever, some muscular pain, and swelling of the neck precede a pink rash, cough, and nasal congestion.

The disease is less contagious than such ailments as rubeola (common measles) and chickenpox. About 1 in every 5 persons reaches adulthood without having had rubella. Thus, a large percentage of women of child-bearing age are not immune to rubella. When such women catch rubella in early pregnancy, it can kill or cripple their unborn children.

Rubella was first linked to birth defects in 1941 by the late Dr. Norman Gregg, an Australian ophthamologist, who traced an unprecedented number of cataracts in babies to a rubella epidemic in 1940. It was later learned that the most dangerous period for rubella infection is the first 12 weeks of pregnancy. In about 20 percent of the expectant mothers who contract rubella during that period, pregnancy ends in spontaneous abortion or stillbirth, or the infant is born with serious physical and/or mental defects. In addition, some babies born with rubella show no symptoms but may harbor the virus for as long as 18 months after birth. In the meantime, they can pass the disease on to others, including women in early pregnancy.

EARLY RESEARCH

Methods for laboratory study of the rubella virus were developed only as recently as 1962. At that time, isolation of the virus and its growth in cell cultures were reported simultaneously by two groups of investigators: Drs. Thomas H. Weller and Franklin A. Neva of Harvard University and Drs. Edward L. Buescher, Paul D. Parkman, and Malcolm S. Artenstein of the Walter Reed Army Institute of Research.

This achievement meant that development of a rubella vaccine was theoretically possible. Since then, investigators in this country and abroad 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, or weakened to the point where it can produce immunity without causing the disease. Examples of these two types of vaccines 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 problems of great complexity. The killed virus vaccine, during the inactivation process, lost much of its ability to produce immunity. And the early live virus vaccines gave equally disappointing results: many of the vaccinated volunteers developed typical rubella and spread the infection to those around them.

COLLABORATIVE EFFORT UNDERTAKEN

It soon became apparent that what was needed to develop a rubella vaccine was an intensified effort. With a special appropriation for fiscal year 1966, the National Institute of Allergy and Infectious Diseases was assigned the challenging task of directing the development of a rubella vaccine.

In early planning, an advisory committee of virologists and pediatricians recommended that the Institute's collaborative research program coordinate the efforts of Government, industrial organizations, and universities in a voluntary partnership similar to that which has worked well in the collaborative effort to develop respiratory virus vaccines.

In addition to eight of the Nation's leading pharmaceutical companies, the NIH collaborative program includes two private research laboratories, two university medical centers a hospital, and certain facilities of the Bethesda, Md., intramural 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 continuing goal of the NIH research attack on rubella is the development of safe and effective vaccines before the next rubella epidemic, which is expected to strike in the early 1970's. The use of a live attenuated vaccine, suitable for mass inoculation of children, would provide a high degree of immunity for long periods of time and thus contribute to widespread control of the disease. But because not enough is yet known about the effect of a live rubella vaccine on pregnant women and their unborn children, it is considered highly desirable that a killed rubella vaccine also be developed. In view of the time riquired to extensively test the safety and effectiveness of any vaccine, the development of both killed and live vaccines is proceeding simultaneously.

THE FIRST PROMISING EXPERIMENTAL VACCINE

There is already a promising live attenuated virus strain which gives great hope for the eventual development of a rubella vaccine.

As a result of increasingly intensive study of rubella by a number of investigative groups, the NIH Division of Biologics Standards established a comprehensive research program in 1964 to prepare for procuring and evaluating the scientific information essential to the testing and licensing of the hoped-for vaccine. Drs. Harry M. Meyer, Jr., and Paul D. Parkman were placed in charge of the DBS program. After 2 years of intensive study, they developed a rubella virus strain which in early trials conferred immunity without transmitting the infection to unvaccinated persons.

In their research, Drs. Meyer and Parkman passed the rubella virus through primary African green monkey kidney cell cultures 77 times. At that point, after a series of successful laboratory tests, the high-passage virus (called HPV–77) was considered ready for animal trials. Of great importance at that stage was the discovery that the HPV–77 strain, when inoculated into rhesus monkeys, resulted in the development of immunity. In addition, there was no indication that the rubella virus was present in the animals' blood or that it spread to uninoculated animals.

These observations clearly showed that the HPV–77 rubella virus strain had been sufficiently modified by tissue culture passage for use as an experimental vaccine. The vaccine was prepared under the same rigorous standards and safety

tests used in the production of live attenuated vaccines for ordinary measles and poliomyelitis. The next step was a clinical trial.

Clinical trials of adequately tested live rubella virus preparations offer little risk if pregnant women are not exposed to the vaccinated persons or to persons infected by contact with them. These precautions can best be carried out in the closed-population environment of institutions where even the movement of personnel is administratively controlled.

The Arkansas Children's Colony, a State educational institution situated in an isolated rural area, met these requirements. There the Meyer-Parkman team conducted pilot studies with the experimental vaccine. They had the full cooperation of the Department of Pediatrics of the University of Arkansas School of Medicine and the staff of the Arkansas Children's Colony, and the written informed consent of the parents of each child involved.

Sixteen girls were selected for the study. All were susceptible to rubella. Eight were inoculated with the high passage virus preparation. The other eight served as controls. All lived in the same cottage in close contact with one another. None of the inoculated girls showed any of the typical signs of rubella such as rash, enlarged lymph nodes, or illness which could be attributed to the vaccine. Also, none developed detectable viremia (presence of virus in the blood), yet all developed virus-neutralizing antibodies indicative of immunity. And none of the uninoculated girls became infected, even though the attenuated virus was found in the nose and throat of some of the vaccinated girls.

These results appeared to indicate that the HPV–77 rubella virus strain was attenuated and produced a noncommunicable, immunizing infection in vaccinated persons. Senior scientists at several universities who were informed about the study all agreed that similar but more extensive trials should be conducted without delay.

The second study involved three cottages and 48 rubella-susceptible children. Twenty-six were inoculated; 22 served as controls. The results of this trial completely confirmed the findings of the pilot study. In the ensuing months, Drs. Meyer and Parkman conducted further clinical studies with their experimental vaccine, and several university groups used the vaccine to confirm the original findings of the DBS investigators. The HPV–77 strain has been made freely available to investigators and to interested pharmaceutical manufacturers in the United States and abroad who are now engaged in research with this and other experimental rubella virus preparations.

The HPV–77 vaccine preparation is promising. But it may not be the vaccine ultimately used for widespread immunization because of the sheding of the attenuated virus from the nose and throat of some vaccinated persons. Further passage of the virus in tissue culture may result in a vaccine that protects without shedding. Varius derivatives of the HPV–77 strain are now being tested to determine if they are superior. This and other work in progress must be completed to reach the long-term goal.

A QUICK TEST FOR RUBELLA

Advances since 1961 in the study of rubella virus have made the control of the disease and its associated birth defects a practical possibility. But comparable progress in the development of diagnostic techniques has been made only recently.

Those engaged in rubella research were well aware of the limitations of the three available serologic procedures. The neutralization test is expensive, complicated, and time-consuming. The fluorescent antibody method, which poses similar problems, provides less reliable results. And diagnostic laboratories are rarely equipped for large-scale use of either test. The third method, involving complement fixation (CF), is less useful. Rubella patients often fail to develop detectable CF antibody; and when it does appear, it is relatively transient. Furthermore, the CF test has no value in live vaccine studies since the attenuated rubella virus does not evoke a CF antibody response.

Drs. Meyer and Parkman and their DBS research team perfected in 1966 a method for measuring rubella immunity. The advantages of their test are its simplicity, speed, sensitivity, and reliability. Also, it is capable of detecting immunity years after infection.

Known as the H-I test (hemagglutination-inhibition), the method is based on the biological principle of hemagglutination (or red blood cell clumping) which has been used successfully in studies on influenza and other diseases. The DBS scientists found that special preparations of rubella virus cause the red blood

cells of newly hatched chicks to clump. When they added a sample of blood from a person immune to rubella, the antibodies in the immune blood inhibited clumping. In short, the absence of clumping demonstrated immunity to rubella.

The new test has a number of potential uses:

Physicians caring for expectant mothers who have been exposed to rubella can rapidly determine whether the women are immune.

Rubella infection can be quickly confirmed even in the absence of clinical symptoms.

When a rubella vaccine becomes commercially available, women could be tested before marriage so that those lacking immunity could be inoculated.

The new technique also promises to speed up the development of rubella vaccines, since the effectiveness of experimental virus preparations in clinical trials can be evaluated far more quickly than with previous techniques.

The new test was reported only a few months ago. But samples of the test materials and descriptions of how they are used have already been distributed to scientists throughout the country and around the world. The Vaccine Development Branch of the NIAID and the DBS group held a special workshop in December 1966 to inform pharmaceutical manufacturers and others involved in vaccine research how to apply the new technique. The test has also been made available to the Communicable Disease Center of the Public Health Service for distribution to diagnostic laboratories across the country. The new test is inexpensive and simple and it should soon be routinely available in hospitals, health departments, and other laboratories.

EFFORTS INTENSIFIED

Armed with increased knowledge and improved techniques, medical science stands on the threshold of a solution to the rubella problem. All available experimental vaccines are now undergoing intensive laboratory and clinical testing for safety and effectiveness before they are tried on large numbers of children. Trials thus far with small groups have shown that the HPV–77 strain did not spread from vaccinated to susceptible individuals in close contact with them. Even if there were undetectable spread, this would not be a problem if pregnant women were not exposed. However, differences in susceptibility due to the subtle body changes which occur in pregnancy must be considered and studied since little is known of the effect of attenuated rubella virus in early pregnancy. Cultures used for rubella vaccine manufacture must be of a type established as safe for human inoculation. If the cell line has not been previously used for other licensed biologics, evidence of its safety must be obtained. While there is no evidence to incriminate the cell strain used as a factor that might cause tumors, the tumor-causing potentiality of viruses in general requires considerably more investigation. In this effort, the various members of the NIH collaborative team are contributing according to their specialized skills.

Of particular importance is the work of industry and university research contractors to refine and modify available experimental live rubella virus vaccines. They are engaged in the following representative activities:

Propagating, attenuating, and characterizing virus strains grown at different temperatures and in different cultures, using a broad range of tissue culture systems.

Investigating the freeze-dry production process to learn whether rubella virus strains can be stored in a dried state without loss of potency.

Studying monkeys inoculated with the HPV–77 vaccine to determine where the virus is reproduced in the body and how it travels from the site of inoculation to the nose and throat.

Developing and testing in laboratory animals a coated capsule containing rubella virus for oral administration. This oral rubella vaccine, now being administered to human adult volunteers, is patterned after the highly successful oral adenovirus–4 vaccine developed by the NIAID.

Attempting to isolate naturally occurring attenuated rubella virus strains from persons with the disease.

Seeking new and improved techniques to measure virus attenuation.

KILLED VACCINE ALSO BEING SOUGHT

The search is also continuing for an inactivated (killed) rubella vaccine since in the present state of our knowledge live rubella vaccine should not be administered to pregnant women. Some contractors are devoting much time to this effort.

Among the inactivation techniques being employed are the use of cobalt irradiation and the chemical formalin. The chemical betaprone and ultraviolet light also are being tried separately and together.

Other workers are evaluating the possibility of employing a sophisticated laboratory procedure to produce a killed vaccine using only the outer portion of the rubella's virus particles.

CONTRIBUTIONS OF FUNDAMENTAL RESEARCH

Valuable contributions to the knowledge of rubella have also emerged from the fundamental research programs conducted and supported by the National Institutes of Health.

For example, at the NIH laboratories in Bethesda, Md., scientists have shed further light on the role of rubella as a cause of infant deaths and defects. In related animal investigations, ferrets are being used in studies of how the rubella virus behaves in the living body. Ferrets are also being used to test hyperimmune rubella gamma globulin, which is sometimes administered to pregnant women exposed to rubella.

NIH grantees also are engaged in the concerted campaign against rubella. Scientists at university medical centers supported by NIH recently confirmed the presence of rubella virus in 64 percent of the fetuses examined in the wake of a rubella outbreak. Other grantee scientists reported recovering the virus from tissue cultures prepared from the placentas of women with a history of infection during pregnancy. And still others found that infants born with rubella excrete the virus for long periods of time in their saliva and urine.

NO TIME TO WASTE

All the people involved in the urgent search for effective rubella vaccines are racing against time. And that time may be only a few short years away. The next rubella epidemic is expected to strike the United States in the early 1970's. Hopefully, by that time a safe and effective vaccine will be available to prevent the epidemic from leaving in its wake thousands upon thousands of dead and crippled babies.

With that goal in mind, the NIH team is moving ahead. The NIAID Vaccine Development Branch is presently engaged in studies with the DBS live HPV–77 virus strain and is continuing its search for killed vaccines. The DBS research group is working in close cooperation with them, and every effort is being made to speed the development of a rubella vaccine that can be licensed for commercial use. The continuing efforts of the Vaccine Development Branch will make it possible for the NIH rubella research advance to be carried into the large-scale studies necessary to achieve the final goal—the eradication of birth defects due to rubella.

VIRAL VACCINES

Dr. SHANNON. So that you won't bump into a controversy a year from now in the holding back of the development of this, it might be worth putting this on the record. There is some evidence to suggest that viral vaccines that are grown in cell suspensions of one sort or another, developed from other than human tissues, have a capacity to cause wild viruses which can interact.

Mr. FLOOD. They are real wild, aren't they?

Dr. SHANNON. And they produce adverse effects that cannot be predicted. The big problem in this particular area is to select a cell system for the growth of the virus that will minimize such a possible hazard.

I would judge from the mail I get and from the conversations I have had with a number of scientists that, at the present time, opinion is divided whether indeed one can avoid such a hazard, or whether the hazard is too great to chance.

This is the reason for the very large program in the Division of Biologic Standards, which Dr. Murray spoke about, for the develop-

ment of knowledge that will permit the elimination of the risk of ill effects from virus vaccines. The implications that these viruses are involved in the development of tumors of a carcinous nature points up the hazards of using these agents in populations that otherwise might not be susceptible. The major safety factor we have is that, generally speaking, these wild viruses don't jump species.

It is difficult to take a virus from one specie and transmit it in small doses to another. One of the ways of making it jump species lines is to use very young animals and to use very large doses. If the resulting vaccine is used for the susceptible mother, you are also exposing to it the prenatal child that might be acutely susceptible to one of these strains that results from the interaction of the wild virus in the live virus vaccine which you are giving.

I think this controversy will become hotter and hotter as the years go on. It is one of the major hazards that will have to be resolved in the development of the vaccine. It is not simply a question of making the vaccine and putting it out. I think we are sufficiently far along now that this can be done. It is the containment of the hazard that must concern us.

SHINGLES

What about shingles?

Dr. DAVIS. This is a strange disease. It is clear now that it is caused by the same virus that causes chickenpox. Just what the action is——

Mr. FLOOD. It seems to affect older people.

Dr. DAVIS. Yes.

Mr. FLOOD. Chickenpox doesn't.

Dr. DAVIS. Chickenpox affects, of course, children. It is a highly contagious disease. It spreads very rapidly.

This is one of the puzzling things. We don't know just what happens to a person who has already had chickenpox, presumably, and then comes down with shingles many years later.

Mr. FLOOD. I have had chickenpox. Am I going to get shingles?

Dr. DAVIS. I think you and any of us would have about the same risk. There seems to be a partial immunity, or a sensitivity, to this virus that we don't fully understand. We do know, though that the virus apparently attacks the nerves because of the distribution of the lesions. They have the same distribution as certain peripheral nerves, largely around the chest, or the middle.

Mr. FLOOD. Years ago you heard about this every day. Do people still have shingles?

Dr. DAVIS. Yes. It is a common disease and a very painful one.

Mr. FLOOD. Male and female?

Dr. DAVIS. Yes. It is not only confined to older people. For instance, my daughter, when she was 14, had it. The medical name is herpeszoster.

ROCKY MOUNTAIN LABORATORY

Mr. FLOOD. You mentioned a few minutes ago something about your Rocky Mountain laboratory. Do you want to brag a bit about that this year?

Dr. DAVIS. Some of the most interesting work in the Institute is going on out at the Rocky Mountain laboratory in Montana. The work on the TB vaccine, which we mentioned earlier, and the extremely

active work out there is determining whether or not certain viruses may cause chronic neurologic disease.

SCRAPIE

We are studying a disease called scrapie, a disease of sheep which has similar pathologic lesions and clinical aspects to multiple sclerosis.

We know that scrapie is caused by a virus. The virus can be isolated; we can infect mice with this virus and reinfect sheep and goats. We hope by using this model that we may either develop an animal system to study the disease or else to devise a way to isolate virus from humans who have diseases which resemble it.

Mr. MICHEL. In the Department of Agriculture appropriation bill we have money for research to combat that disease of sheep. Is there any rapport between your shop and those people in ARS in something like this?

Dr. DAVIS. We have a great deal of rapport. As you know the Department of Agriculture has strict quarantine regulations and very strict containment regulations for studying scrapie. The virus cannot be introduced into the country except at special places. In developing our animal facilities, we consulted with officials of the Department of Agriculture very closely to see that our facilities were satisfactory to them. Our scientists also have communication back and forth on research matters. In fact, we have received a lot of information about the disease from Department of Agriculture scientists. There is a lot of communication.

Mr. FLOOD. Does this affect the older sheep as well as the lamb?

Dr. DAVIS. It has a long incubation period; about 3 years in sheep.

Mr. FLOOD. Are you having trouble with our friends in New Zealand and Australia about that?

Dr. DAVIS. No—I am not familiar with the problems of importation.

GORGAS MEMORIAL LABORATORY MALARIA PROGRAM

Mr. FLOOD. What is going on at the Gorgas Memorial Laboratory?

Dr. DAVIS. The Gorgas Memorial Laboratory has several active programs including one on malaria which, as you know, is an important disease in Central America. The director of the Laboratory, Dr. Martin Young, is a malariologist and has worked in the field for many years.

Mr. FLOOD. Is there any stateside malaria?

Dr. DAVIS. The only malaria we have in the United States now is that which is imported into the United States. Actually——

Mr. FLOOD. How about troops coming back?

Dr. DAVIS. Yes. Largely from Vietnam. Or citizens coming back from Africa or other parts of the world where malaria exists.

About 150 cases were reported in the first 6 months of 1966.

Mr. FLOOD. What is the incubation period?

Dr. DAVIS. It varies. It is usually about 14 days.

Mr. FLOOD. It will recur?

Dr. DAVIS. There are relapses. There may be relapses up to 7 years. Usually it is within 9 or 10 months and often 2 or 3 years but may be as long as 5 or 6 years.

MIDDLE AMERICA RESEARCH UNIT

Mr. FLOOD. Would you like to say something about the Middle America Research Unit?

Dr. DAVIS. This is a direct operation of the Institute staffed by our own people. They are primarily concerned with viruses transmitted by insects, chiefly mosquitoes. At the present time MARU is making a comprehensive survey of serum from all parts of Central America to determine the importance of human disease caused by arboviruses.

Mr. FLOOD. What significant work has come out of this operation?

Dr. DAVIS. About 2 or 3 years ago the group down there investigated a strange disease that occurred in Bolivia, known as Bolivian hemorrhagic fever.

We studied this because it was very similar clinically to a disease occurring in Korea during the war known as Korean hemorrhagic fever, for which the cause was not found. We believed there were sufficient similarities to get some leads. Actually, for the disease occurring in Bolivia and in other parts of South America, our staff did find the cause and were able to demonstrate how it was transmitted and to institute control measures. We have now assigned one of our virologists to Japan to work with the Army there for the specific purpose of investigating Korean hemorrhagic fever.

Mr. FLOOD. Is this a blood disease?

Dr. DAVIS. The virus does occur in the blood. The infection comes from rodents, little mice which apparently live in the environs. They excrete the virus in the urine and feces, and contaminate the surroundings in the primitive conditions in which the people live. Food and clothing is contaminated and the individuals get the disease.

TOTAL PROGRAM LEVEL FOR 1968

Mr. MICHEL. Doctor, looking at page 264 of our bill and some of the figures we show, if we look back to the year 1965, the National Institute of Infectious Diseases, we see an estimate of $68-million-plus. Actually the appropriation was nearly $70 million. For 1966 the request of just a shade under $75 million and the appropriation was $78 million; and in 1967 the request was for $85 million-plus, and an actual appropriation of $90,670,000. There seems to be a pattern of more actually being appropriated than requested.

I see for the year 1968 you are up to $94,422,000; in footnote 3 it says, "Excludes money transferred in the estimate for General Research and Services, NIH."

Does this mean that for your activities you are up to practically $100 million?

Dr. DAVIS. That is correct. The transfer for 1968 and 1967, too, is $4.5 million for the United States-Japan program which is being shown under the Office of International Research.

Mr. MICHEL. Expand on that a little, if you will.

HISTORY OF BUDGET REQUEST

Dr. SHANNON. I would like to point out in the same table on page 206 of the justification it shows the appropriations actually made available and the estimates sent by the Department to the Bureau of

the Budget. It seems that there is substantial agreement between those estimates and the appropriation. Basically, Congress restored the funds cut by the Bureau of the Budget. The request is a curtailed request.

Mr. MICHEL. Do we have in the record how much of a curtailed request?

Dr. SHANNON. I am not talking about the request of the Institute and the Public Health Service, and so on, but the Department estimate to the Bureau of the Budget of $102,682,000. The Bureau of the Budget felt that because of the stringent situation that obtained they could not request of the Congress more than $94,422,000. So the Bureau of the Budget, in effect, cut the Department's request by approximately $8 million.

You will appreciate that the Institute has to justify its request to us; we to the Public Health Service; the Public Health Service to the Department; so by the time this figure goes to the Bureau of the Budget it is a sound, "technically arrived at" figure. The question which the Bureau of the Budget then has to decide is the allocation of resources. In these programs, this year, they felt we could do what is shown here.

EFFECT OF FURTHER BUDGET REDUCTION

Mr. MICHEL. When that went to the Bureau of the Budget and was scaled didn't your shop feel that this necessarily was going to curtail and cut back activities that just have to be done? In other words, was there really a hue and cry because the Bureau of the Budget did it?

If we take the same line in this committee and say, "There wasn't too much of a cry there, they cut back $8 million, and we are in a bind up here, too, we will look at this requested figure and take another $8 million." Then what happens?

Dr. SHANNON. The Bureau of the Budget took this cut, fully realizing that we would not be able to take advantage of many opportunities that were provided for in the Department's submission. It is my own conviction that if any of these items are cut below what they are at the present time, it would have disastrous effects on the programs.

Mr. FLOOD. Disastrous?

Dr. SHANNON. Disastrous; yes, sir.

Mr. FLOOD. Do you use that term advisedly?

Dr. SHANNON. I do, sir; yes. I think the number of trained scientists who are coming into the field who will not be supported with these appropriations is very substantial. I think this will have an effect on the plans of new young scientists just beginning their careers; it will divert some of them from careers in the biomedical sciences. I think if you take an already curtailed budget and cut it further, that this will have a very profound effect on the programs.

GENERAL CLINICAL RESEARCH CENTERS

Some of the programs are already cut below what I consider to be a subsistence level.

Mr. MICHEL. Could you single out any specific areas?

Dr. SHANNON. You may want to discuss this at some length with Dr. Kennedy when he comes. His budget proposes an increase for "General clinical research centers" from $28.5 million to $30.5 million. This is the primary program in all of NIH that is aimed at the translation of laboratory knowledge to clinical knowledge for direct application to disease. It catalyzes our entire effort at social application.

The Senate last year indicated that it was their desire that we should extend these clinical research activities to encompass not only the study of inpatients, but the study of outpatients. During the past year, there have come into being other medical centers that require resources. We feel that we could not withhold those resources, so we take the funds available and let them share and share alike at somewhat reduced levels.

I say, "somewhat reduced levels" because 70 percent of these funds are for hospital care of clinical patients. In the past year hospital costs have gone up by 16 percent. It is projected that next year they will go up another 15 percent to 16 percent. This has nothing to do with medicare. This is largely due to legislation such as minimum wage laws; it is due to the drive of many of the paramedical professionals to acquire a living wage.

If you take the program of 30.5, an increase of $2 million——

Mr. FLOOD. This is April of 1967 that you are talking about?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. And it may be June before the Congress takes final action on this.

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Are you suggesting that this is precarious since it was born back in October and has become progressively worse? Disastrous?

Dr. SHANNON. Yes, sir.

Mr. FLOOD. Do you read election returns?

Dr. SHANNON. We have already cut back on some of these programs. With two 15-percent-plus increases over a 2-year period, we will have to cut back further, which will result either in a lesser amount of clinical investigation of this type or in the schools having to go out and find the money elsewhere and I don't think they can. Any cutting in an item such as that—and these items are interrelated—will have disastrous effects.

What will happen is that the scientist who has a program ready to enter the clinic will find that the resources for clinical trial are not available. He will be able to transfer some of the money from his grants for his patients in that type of hospital center, so the only way of buttressing what is inadequate support for the clinical centers will be for the individual investigator, on a case-by-case basis, to ask for money. That is why I say this is in a very precarious state and that any substantial cut, in almost any of the programs, will have repercussions right across the board. I can't make that statement strong enough. I am not making a plea for any substantial increase of any item. I realize the basis for the cuts that were made by the Bureau of the Budget and I can't quarrel. It is their responsibility to decide how resources shall be spent. But I consider this budget as less than a bare bones budget. Please believe me, if this committee recommends cuts below what they are now, they will do very serious damage to many areas of medical science.

HOSPITAL COSTS

Mr. MICHEL. Let me go back to be sure I got the figure correct. Did you say hospital costs this past year, or in this coming year, are increasing at the rate of 16 percent?

Dr. SHANNON. It is estimated they will increase this year, I think the figure is 16 percent. I will be very glad to furnish a precise figure and the source of the figure. It is estimated they will increase by a comparable amount next year. I would be very glad to quote the precise figure and the source of the figure.

(The information follows:)

In 1966 hospital daily charges rose 16.5%, according to "A Report to the President on Medical Care Prices," from the Department of Health, Education, and Welfare, February 1967.

Dr. SHANNON. I said that of the $30.5 million for the general clinical research centers 70 percent is for reimbursement of hospital costs.

Mr. MICHEL. Any program where you have this reimbursement of hospital costs involved, we are faced with the prospect that the built-in increases will have to be reflected in one way or another.

EFFECT OF BUDGET REDUCTIONS

Mr. CARDWELL. Mr. Michel, I wonder if I could comment on this question from a budget management standpoint?

You indicated that you thought with some degree of ease we got out $8 million and would a similar cut be acceptable in this committee.

Mr. MICHEL. May I back up a little bit and state further that I have a good idea of what happened to NIH's proposal to the Department, what took place, and then from the Department to the Bureau of the Budget.

Mr. CARDWELL. Taking NIH as a whole, going from the Surgeon General——

Mr. MICHEL. Just in the division we are talking about now, the allergies and infectious diseases.

Mr. CARDWELL. In allergy and infectious disease, the Department reduced the request by $582,000; the Bureau of the Budget by $1,664,000.

Mr. KELLY. The point I wanted to make was, every time you consider a budget, you consider whether or not there are certain new or enlarging and expanding activities that are desirable and whether or not, putting them against other competing demands, you may proceed. These are hard choices when you decide not to do desirable things, not to expand areas where you don't question that it would be profitable. You just don't think it would be as profitable as some other area.

I think you face an entirely different question though when you are faced with the decision as to whether or not you will retrench below the level at which you are now suporting the operation. As Dr. Shannon indicated, by and large the budget that you are considering for the National Institutes of Health is a modest budget. The preponderance of the increase is a built-in increase. It is the cost of carrying for a full year the activities launched this year with only modest adjustments in specific programs.

Therefore, if you make the kind of reduction that you ask for——

Mr. FLOOD. You are below 8 percent.

Mr. KELLY. That is right, and what you would then be doing is that you would be making a cut into an ongoing program. You would be taking resources that have already been applied to these medical resource development programs, the development of facilities, the development of manpower, and initiating research activities and bringing them to a halt. You would be taking resources that have already been invested in this area and making them less than worthless.

It would seem to me—I would not recommend it, but it would seem to me if a decision was going to be made that a lesser amount of resources were going to be invested in federally supported medical research, that this would be done on a long-term basis and that it wouldn't be done with a meat-ax approach; it wouldn't be done on a just fast cut-and-reduction basis. It seems to me this would be a waste of investment that has been made in this field that is important.

Mr. MICHEL. What you are suggesting is that it is much easier to make a reduction in a proposed new area of expenditure. I am inclined to think that too often members of our committees and subcommittees sometimes put too much emphasis on the new proposals and turn our backs on so many of the ongoing programs, simply because they have been there for any number of years.

I am not against progress by any means and sometimes it seems to me increases are warranted in new fields and new areas and are probably much better spent there. I would hate to see an attitude in this field of medical research where everything is changing so quickly and fast that we would just find ourselves locked into some old, going programs because we have been doing them for 10 or 20 years. The thought is "these fellows will not question that because we have an experience table."

Mr. KELLY. I think we should be held accountable for our stewardship of what we are doing with old resources and old programs. The point that I would like to make is that I think you have to be very selective in your decisionmaking. I think the talk about across-the-board reductions in these kinds of programs could have a disastrous effect. They could have an effect that you didn't want to have. When you say or decide that there is an old, ongoing program that isn't worth continuation, that it is not as good as a new program, this should be done quite selectively. It should be done because you have evaluated a specific item and decided not to go ahead with it rather than saying, "Let's just take $2 or $8 million out of this account below the current ongoing level of activity."

Mr. CARDWELL. Your suggestion that you apply that objectivity to both old and new is good. It is probably wrong to try to make an arbitrary distinction between all old or all new. The selectivity must be applied across the board.

Dr. SHANNON. I would like to make a point before we get too far down the line in talking about old and new. I would point out that the bulk of our programs are new programs, that they have not been in existence long enough to pay off; that the substantial rise in the activities of the National Institutes of Health didn't start until 1956 and became apparent in the budget for 1957; that by 1960 we were at substantially less than 50 percent of our current operating level and

many of the current programs started since that time. Many of our research programs have been initiated since that time and we are just getting into the period of productivity. The payoff has not come, but will come in the next 5 years.

I am concerned. When one talks about old line operations, one usually talks about operations that have been in being for 20 or 30 or 40 years and one wonders why they are still there. These are new programs. An indication, at this particular point in time that the Congress is disenchanted with an operation that hasn't had the time to pay off would be catastrophic. I mean that literally.

MEDICAL LIBRARY RESOURCE SUPPORT GRANTS

Mr. MICHEL. In a U.S. Public Health Service research grants and awards booklet announced in February 1967, there are 67 pages listing many different research grants. One item kept cropping up, Dr. Shannon, on medical library resource support. I see at the University of Alabama there is one for $26,000. I see "Medical Library Resources Support, $24,000" at the University of Arkansas. I see one for Los Angeles. I see another one, California—Los Angeles. Same title, different figures.

Then down here we have California—San Diego. All through this—I haven't got the exact number, but what would account for all these medical library resource support grants spread all around the country? Are these people all working on the same thing? What is this?

Dr. SHANNON. This is the National Library of Medicine activity and not National Institutes of Health.

Dr. STEWART. This is a listing of the Public Health Service. Those are grants under the National Library of Medicine authorized by the Medical Library Assistance Act. There is a whole series of medical library resource grants which Dr. Cummings will be defending when he appears before you.

NAMES OF RESEARCH GRANTS

Mr. MICHEL. Your information shows a total of 59 new research grants totaling $1 million-plus. We have had a problem sometimes when we get to the floor with some of these fantastic names that you have conceived for some of the grant programs. I am glad to see as I look through here most of them can pretty well be defended, if for no other reason, on the strength of the technical medical terms that are used.

I see the one, here at Auburn University, Robert S. Berger: sex pheromones of ticks, $23,000. What are we trying to find out there? Have you any idea?

Dr. SHANNON. We will look at the project and tell you precisely what it is all about.

(The information follows:)

The purpose of this project is to determine if, like many insects, ticks possess potent attractive chemicals (sex pheromones) that could be utilized to develop better and safer tick control methods. If such pheromones exist and can be synthesized, they would be used to attract ticks to specific places where they could be eliminated. The pheromone could be applied in combination with insecticides or with other killing devices, or with chemicals that sterilize and

distrupt the reproduction of ticks (chemosterilants). Widespread applications of insecticides would not then be necessary. Treatments could be restricted to small controlled areas. Some principles by which attractants might be used to replace conventional insecticides have been outlined in a special report by the U.S. Department of Agriculture (ARS-22-85; 1963) and, in fact, this method is now being used for practical field control of the cabbage looper caterpillar, an important agricultural pest.

Mr. MICHEL. Just so there is a good explanation for it.

UNITED STATES-JAPAN PROGRAM

Here is one at UCLA. It amounts to $99,000. It is the largest one at UCLA, basic research on filariasis in the Southwest Pacific.

Dr. DAVIS. This is a part of the United States-Japan program. Filariasis is an extremely important disease in Soutseast Asia.

Mr. MICHEL. There are several other places, like New Guinea, identified here. Does that all fall within that same category?

Dr. SHANNON. Yes, sir. The Japanese program is a combination of filariasis-schistosomiasis diseases, certain virus diseases, tuberculosis, leprosy, cholera, and malnutrition. This is the group of diseases that come under that program. The total that it is planned to spend, largely in this country, is, I believe, $10 million this year.

Mr. SHRIVER. How much is Japan spending for this?

Dr. SHANNON. It is very difficult to tell, Mr. Shriver. They keep their books differently. They have three sources of funds. Their academic establishment, the medical schools and professional schools, are supported by the department of education. The public laboratories that relate to health programs or health problems are supported by the health department. Then they have a group of committees, like Japanese Science Committee, or a commission, where they channel funds.

In the aggregate I might say they are spending substantially less than we are, but I would point out that although this is a collaborative operation, they are spending their money for their scientists and we are spending our money for our scientists for a commonly agreed-upon purpose.

Mr. SHRIVER. It is a cooperative program?

Dr. SHANNON. It is scientific cooperation that involves no exchange of dollars.

Mr. SHRIVER. I am on the Appropriation Subcommittee for Foreign Aid and I was interested in asking this for that reason. We have aid all over the world in one way or another. A lot of it is not even known about.

Dr. SHANNON. We would be glad to give this committee a short report on this operation.

The characteristic of the agreement worked out with the Japanese was that an arrangement would be developed under which we would support American scientists in doing their work; they would support Japanese scientists in doing their work. We would agree on certain selected goals that had broad importance in an area of common interest in Southeast Asia.

INFECTIOUS DISEASE RESEARCH IN OTHER COUNTRIES

Mr. MICHEL. Doctor, do you know of any foreign country that is doing more than the United States in your general field of activity?

Dr. DAVIS. No; I think we have had the largest total program in the world. This would be in all areas of infectious diseases.

Mr. MICHEL. Could you single out two countries that rank second or third to us, in other words, that are doing an outstanding, commendable job in this field?

Dr. DAVIS. The British scientists for years have been extremely important in developing new knowledge on virus diseases. This goes back to the days when Dr. Christopher Andrewes and his associates identified influenza virus, in 1933. British scientists worked out the characteristics of a group of viruses known as rhinoviruses which we now know cause about 50 percent of the common colds.

European scientists have been active in the field of tissue transplantation and organ transplantation. Dutch workers in Amsterdam and Leyden have been in the forefront of developing the tissue typing system of matching tissue cells so that we have much better success in transplanting organs.

Mr. MICHEL. And how about Japan itself?

Dr. DAVIS. Japanese are very active. We talked about tuberculosis. They have been especially active in the chemical immunology of tuberculosis. In fact, they are ahead of American scientists in this. We have learned a great deal from the Japanese scientists about tuberculosis under the United States-Japan program, through mutual conferences or visits. We have gained a lot from them in this particular field.

Mr. MICHEL. That is all, Mr. Chairman.

COMMON COLD

Mr. HULL. Dr. Davis, what are you doing about the common cold?

Dr. DAVIS. Work on the common cold has been very active. I just mentioned that we now know the cause of about 50 percent of common colds. It is a group of viruses known as the rhinoviruses. Unfortunately, there are many members of this group. Fifty-five have already been identified, each one slightly different. This means even though you get a cold one winter, you might get another within a year or so. It would take quite a few years to run the entire gamut. That is the reason why people have so many colds repeated year after year. There are all different kinds of viruses. Actually we still can't identify the cause of about 50 percent of these infections.

RUBELLA VACCINE

Mr. HULL. It was a Senate report that asked that work be done on Rubella vaccine development to proceed as quickly as possible so that an effective, safe vaccine will be available well before the 1970 epidemic and the committee has added $500,000 to the funds budgeted for Rubella vaccine development. Is that the German measles?

Dr. DAVIS. Yes. We have a large contract program that now consists of 15 different contracts, four of them in universities, which are supporting development of rubella virus vaccines. The work is still very much in the developmental and experimental stage. The candidate vaccines need to be safety tested; they need to be evaluated in animals and we need better animal models in which to develop tests for evaluating them. They need to go into small groups of people and finally into larger groups.

Dr. SHANNON. I think Dr. Davis has been so close to the problem that he doesn't emphasize that when one has a number of contracts out in an area such as this——

Mr. FLOOD. He means you are so close to the trees you can't see the forest.

Dr. SHANNON. There are three basic problems. One is to find a test for immunity in order to determine who indeed does require a vaccine. The second big problem with this virus is that it doesn't grow well. You can't harvest large quantities for either inactivation or modification.

The third problem is to test a variety of strains for their antibody production without, at the same time, running a serious risk of infecting people close by.

The problem of a vaccine of this sort relates particularly to the latter. When you choose to immunize a population of schoolchildren because they are susceptible, most of their mothers will be of childbearing age. If you give them a vaccine which easily spreads to the population group they are most exposed to, the chances are very good that you will infect the mother. The chance is that she is in the age group where the possibilities of pregnancy are quite high and you get into a situation of precipitating the very thing you are trying to prevent.

A series of contracts of this sort will have perhaps three major themes of this sort, each one supplementing the other, and indeed, involving a certain amount of parallel programing because, while the drive at the present time is for a live virus that would give permanent immunity, nonetheless, short of that, one wants a killed virus that would produce at least temporary immunity. It is, therefore, a complex contract program. When Dr. Davis says he has a very large program, sir, I would disagree. He has a very modest program in relation to the importance of the disease.

Mr. HULL. How far back in years does this German measles go? It seems to me I heard about that when I was quite young—much younger than now at least. How long have we known about it?

Dr. SHANNON. The virus of German measles was isolated by a group of people some 4 years ago.

Dr. DAVIS. In 1962.

Dr. SHANNON. The opportunity to move in on the disease didn't come until the virus was actually isolated.

Mr. HULL. How often did this epidemic happen then?

Dr. DAVIS. About every 8 or 9 years. There is an epidemic of varying severity about every 8 or 9 years. In 1964 and 1965 it was exremely severe, the most severe epidemic on record, but the period before that it was not particularly severe.

Mr. FLOOD. But it is very short in duration?

Dr. DAVIS. The disease?

Mr. FLOOD. I mean the epidemic.

Dr. DAVIS. It lasts several months.

Dr. SHANNON. What happens, Mr. Chairman, is that it wanders around the country as it spreads.

Dr. DAVIS. In 1964 it was predominantly here on the east coast and the central United States.

Mr. FLOOD. It was much shorter than that. Bad, but short, I thought.

Dr. SHANNON. It is usually bad and short in a given locality, but when you look at the country as a whole, it stretches out.

Mr. HULL. Where did it come from originally?

Dr. DAVIS. It has been with us always.

Mr. HULL. It didn't start in some other country?

Dr. DAVIS. It is a disease and a virus which has been with us as far as we have any medical records.

VIRUSES

Mr. HULL. In your statement you say, "Should certain biochemical changes take place—" then you go on "still another possibility is that the virus genetic material (DNA or RNA) may take over control of the machinery of the host cell. Instead of reproducing itself, causing an acute infection, and killing the cell, the virus may transform the cell. The result is cell growth gone wild—or cancer."

Would you explain that?

Dr. DAVIS. In animals viruses can infect the animal and infect the cell and actually change the cell so that it will then cause a tumor. This occurs not only in mice, but also in chickens and even in cattle.

Now, this can be reproduced in the laboratory using tissue culture techniques by growing just a sheet of the cells. By introducing viruses to this exerimental situation, you can show that the virus penetrates the cell itself and even the nucleus. The viral genetic material will then control that cell and will change it. It changes its character of growth. This may be one of the factors in the development of human cancer.

Mr. HULL. In other words, it is the bane of our existence, the viruses.

Dr. DAVIS. This is a most important problem. It is the area in which we have probably made the most advances in the infectious diseases in the last 10 or 15 years because of new techniques of growing and identification of new viruses.

Mr. HULL. And separating them.

Dr. DAVIS. Separating them from each other.

Mr. HULL. That is all, Mr. Chairman, thank you.

Mr. CASEY. Do you do any work on venereal disease?

Dr. DAVIS. No, practically none. We have a few grants. Just an occasional grant.

Mr. CASEY. You mentioned it in the first part of your statement. I just wondered if you had any.

Dr. DAVIS. This is all done by the Division of Venereal Disease in the Communicable Disease Center.

ASTHMA

Mr. CASEY. Has anyone gone into the asthma situation with you, Doctor?

Dr. DAVIS. Asthma comes under the aegis of our institute.

Mr. CASEY. Are we making any progress in that field?

Dr. DAVIS. Not as much as we would like. We know that asthma, as it occurs characteristically in children and young adults, depends upon a basic antibody reaction, something like hay fever. Many

people seem to outgrow this condition as they get older. There are also pharmacologic mechanisms that take place in the disease. These are being studied.

Mr. FLOOD. I am a coal miner. You don't outgrow asthma. It is progressive in adults.

Dr. SHANNON. Mr. Chairman, too frequently asthma is used as a generic term to cover chronic respiratory disease.

Mr. FLOOD. I didn't know in what sense Mr. Casey was using it or the doctor, but you know there are men who went to high school with me who suffer from it. They went into the mines. I went to college. I was one of the lucky ones. If you saw them sitting in the kitchen in their homes in my town—while they are my age, they look 80 years old. We call that anthrasilicosis really.

Dr. SHANNON. Dr. Davis used the term in the specific sense——

Mr. FLOOD. I guess Mr. Casey is using it the same way.

Mr. CASEY. That is right, and I have never been a coal miner.

Is it hereditary?

Dr. DAVIS. There seems to be a hereditary predilection for asthma. A large number of individuals have this disease in the country.

Mr. CASEY. It is not caused by a virus?

Dr. DAVIS. No; it is caused by a sensitivity to an allergen. This is the primary cause. A sensitivity to an allergen in the same way one is sensitive to hay fever pollen or to poison ivy, but it affects the bronchioles and the bronchi of the lungs.

Mr. FLOOD. Coal dust is an irritant. It is the result of a direct irritant.

Dr. DAVIS. This is a later stage of the condition.

I have some figures about the number of cases of asthma if you would like me to put them in the record. There are 5,400,000 persons in the United States now affected with asthma. Three million of these are under 16 years of age.

Dr. SHANNON. That is using asthma in the highly restrictive sense, not in the sense that the chairman is using it.

Mr. FLOOD. Am I using the wrong word?

Dr. SHANNON. I believe you are, sir; because you are dealing with two entities.

Mr. FLOOD. We called this asthma all my life. I never heard of anthrasilicosis until a couple of years ago.

Dr. SHANNON. It is the so-called miners disease. The asthma Dr. Davis is talking about relates not at all to miners disease, as such, although some of the symptoms are identical.

Mr. FLOOD. In World War II, with Seabees using jackhammers making runways on the coral islands in the Pacific, we picked up a lot of this in the Veterans' Administration.

Dr. SHANNON. Any number of chemical agents can bring about these symptoms.

Mr. FLOOD. They all look and sound and act exactly alike.

Dr. SHANNON. This is right because you are dealing here with pulmonary insufficiency. Imposed upon that is myocardial insufficiency and the difficulty is a result of insufficiency of the lungs, insufficiency of the heart; and the general symptomatology, regardless of cause, ends up to be the same. But there are three distinct areas. There is the anthrasilicosis type thing, the chronic bronchitis, and emphysema that is more related to infection, and then there is the allergy.

Mr. FLOOD. How would you get that down in Houston, Mr. Casey? Would it just be air pollution?

Mr. CASEY. It wouldn't have to be air pollution. Some of these allergists will say, "You are allergic to house dust." Well, what are you going to do? Move out?

Mr. FLOOD. Or chicken feathers.

Mr. CASEY. Or dog or cat hair. We only have two carpets in our whole house and only foam rubber pillows and things of that nature and we don't have the trouble we used to have and I don't support an allergist any more. My boy has about outgrown it. My wife developed it after we were married.

I don't know what they do now, but they used to make their back look like a pincushion where they injected samples of different things to see the reaction to house dust, cat hair, dog hair, chicken feathers, and everything under the sun. Sometimes they will change their diet, take them off of eggs, or chocolate, or something of that nature.

I used to have to send my wife and my oldest boy up to the hill country about 6 weeks every year so they could breathe. Then they would get over it.

Mr. FLOOD. Why would that be?

Dr. SHANNON. The type of reaction Dr. Davis was talking about is specifically due to what is called an allergic response to an external allergen, or an external substance. Pollen, goldenrod, ragweed, dust, dog hair, or any one of a variety of things.

Mr. CASEY. I started to move off the gulf coast and the doctor said, "Don't do that. You might get up in the hill country where you send them but when the cedar starts getting ripe it might be worse, so you might as well sweat it out," which is what I did.

Is there any solution to this, other than the methods that have been used, trying to improve the environment in which they stay and trying to eliminate the irritants?

Dr. DAVIS. I am sorry to say we don't have any significant advances, and we know so little about the underlying mechanism of the disease. Just why does this irritant produce this kind of a reaction? There isn't a scientific base for any more effective therapy than we have had, or for any prevention—desensitization has been tried with questionable success. Some drugs are helpful. The antihistamines have been found to be helpful in certain people and at certain times. This is about as far as we go.

The Children's Asthma Research Institute and Hospital in Denver has been a pioneer in the study of asthma and in the care of these children. They are providing a situation in which most of the children seem to do very much better and we hope that from clinical studies like this related to laboratory studies, fundamental studies, that we will make more progress in the future than we have in the past.

We are actually putting quite a bit of effort into the solution of the problem. The Institute now supports 19 grants for a total cost of $448,000 under the general subject of airborne allergy, which is what we are talking about.

Mr. CASEY. I know it is something that is puzzling and so far as I can see it is a question of getting the right environment and keeping the irritants away from the patients.

We tried the diet method and that didn't do any good. I think my older boy outgrew most of it. My wife overcame it. She had hay fever and other reactions prior to when she started getting the really strong asthma attacks, where they would put her in the hospital and give her oxygen and things of that nature, but she got over that. I don't mind saying it was a patent medicine that helped more than all these shots we used to give her daily. The doctor said he knew about it and sometimes it helped, but he never advised us about it. We still have confidence in him because he has been in many instances very helpful to other of my friends.

I don't have the problem, but my in-laws have it, my wife has it and about half of my kids have it in some degree. I figured it must be hereditary.

Mr. DAVIS. This seems to be a common pattern, that it runs in families.

Mr. CASEY. I believe that is all, Mr. Chairman.

Mr. FLOOD. Mr. Smith?

Mr. SMITH. What action was taken to insure that the many participants in the NIH collaborative program were not duplicating and overlapping one another?

Dr. DAVIS. The work scope of the contract proposals are reviewed for specific objectives and procedures with NIAID staff and by the Vaccine Development Committee, which is the technical review group of the program, and finally by the Institute's Contract Review Group. This is done to be sure that important aspects of the development are covered in sufficient detail, that there are no gaps in the effort, and that truly duplicative procedures are avoided. An essential element is the rapid reporting of progress between the various contractors by workshops, meetings, and by U.S. Government Research and Development Reports published by the Clearinghouse for Federal, Scientific and Technical Information.

GOVERNMENT PATENTS

Mr. SMITH. There have been press reports that the Merck Co. and your division of biologics standards have developed a vaccine to the same stage at the same time. Isn't this evidence that coordination could be more effective in this program?

Dr. DAVIS. Merck & Co. in November 1966 announced the development of an attenuated strain of rubella virus grown in duck embryo tissue which is presently being evaluated on a small scale. Drs. Parkman and Meyer of the division of biologics standards in April 1966 reported details of the development of an attenuated strain of rubella virus grown in monkey kidney tissue culture, which has now been tested as an experimental vaccine in studies of over 100 individuals. These scientific developments by Merck and DBS represent quite different approaches to the rubella problem and do not indicate a lack of coordination. Much work remains to be done on these experimental vaccines before they could be considered for large scale trials and eventually licensing. It is possible that an improved product can be developed by continued efforts.

Mr. SMITH. What steps have been taken to protect the Government's property rights in the HPV–77 vaccine developed by DBS and to insure that it will continue to be freely available at reasonable costs rather than becoming the monopoly of a single company?

Dr. DAVIS. The invention has been reported in accordance with Government regulations and a patent applied for on December 20, 1966, and assignment recorded to the Government. Licenses will be granted to all applicants on a nonexclusive royalty-free basis.

Mr. SMITH. What steps have been taken to protect the Government's rights in the discovery of the important HI test for measuring rubella immunity?

Dr. DAVIS. The invention has been reported in accordance with Government regulations and the determination made that a U.S. patent application shall be filed by the Department of Health, Education, and Welfare. Such an application is in process of being filed.

Mr. SMITH. What procedures will NIH follow to protect the public's interest in any other patentable discoveries that result from additional research in this field?

Dr. DAVIS. An official inventions report by the scientist concerned must be filed with the Department of Health, Education, and Welfare for appropriate action whenever there is any development that has a potentiality of being patentable. The Department of Health, Education, and Welfare then determines whether a patent should be sought or whether the invention should be published in scientific literature.

Mr. FLOOD. If there are no more questions, we thank you very much, gentlemen.

JUSTIFICATION MATERIAL

National Institute of Allergy and Infectious Diseases

Amounts available for obligation

	1967	1968
Appropriation	$90, 670, 000	$94, 422, 000
Comparative transfers within NIH	−3, 250, 000	0
Transfer to "Operating expenses, Public Buildings Service," General Services Administration	−12, 000	0
Total	87, 408, 000	94, 422, 000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research	--------	$49, 006, 000	--------	$52, 936, 000	--------	+$3, 930, 000
General research support grants	--------	(4, 576, 000)	--------	(5, 325, 000)	--------	(+749, 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
Fellowships	--------	3, 700, 000	--------	4, 267, 000	--------	+567, 000
Training	--------	9, 103, 000	--------	9, 251, 000	--------	+148, 000
Direct operations:						
Laboratory and clinical research	556	12, 488, 000	567	13, 746, 000	+11	+1, 258, 000
Collaborative research and development	33	9, 954, 000	35	11, 025, 000	+2	+1, 071, 000
Biometry, epidemiology, and field studies	80	1, 289, 000	80	1, 356, 000	0	+67, 000
Review and approval of grants	57	1, 358, 000	57	1, 482, 000	--------	+124, 000
Program direction	25	346, 000	25	359, 000	--------	+13, 000
Total obligations	751	87, 244, 000	764	94, 422, 000	+13	+7, 178, 000
Unobligated balance, reserve	0	164, 000	0	0	0	−164, 000
Total, obligations and balance	751	87, 408, 000	764	94, 422, 000	+13	+7, 014, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	751	764	+13
Full-time equivalent of other positions	5	6	+1
Average number of all employees	712	720	+8
11 Personnel compensation:			
Permanent positions	$6,063,000	$6,133,000	+$70,000
Positions other than permanent	39,000	51,000	+12,000
Other personnel compensation	133,000	133,000	0
Total personnel compensation	6,235,000	6,317,000	+82,000
12 Personnel benefits	704,000	718,000	+14,000
21 Travel and transportation of persons	270,000	300,000	+30,000
22 Transportation of things	60,000	60,000	0
23 Rent, communications, and utilities	198,000	210,000	+12,000
24 Printing and reproduction	5,000	5,000	0
25 Other services	1,270,000	1,300,000	+30,000
Project contracts	9,220,000	10,900,000	+1,680,000
Payment to "National Institutes of Health management fund"	4,976,000	5,479,000	+503,000
26 Supplies and materials	2,000,000	2,177,000	+177,000
31 Equipment	515,000	520,000	+5,000
41 Grants, subsidies and contributions	61,809,000	66,454,000	+4,645,000
Subtotal	87,262,000	94,440,000	+7,178,000
Deduct quarters and subsistence charges	−18,000	−18,000	0
Total obligations by object	87,244,000	94,422,000	+7,178,000

Summary of changes

1967 enacted appropriation	$90,670,000
Comparative transfers within NIH	−3,250,000
Transfer to "Operating expenses, public buildings service," General Services Adminstration	−12,000
Unobligated balance, reserve	−164,000
1967 total estimated obligations	87,244,000
1968 estimated obligations	94,422,000
Total change	+7,178,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built-in:				
1. Annualization of new positions authorized in 1967				$59,000
2. Annualization of wage board pay increases				15,000
B. Program:				
1. Research grants		$49,006,000		3,930,000
2. Fellowships		3,700,000		567,000
3. Training		9,103,000		148,000
4. Laboratory and clinical research	556	8,504,000	11	828,000
5. Collaborative research and development	33	9,909,000	2	1,052,000
6. Biometry, epidemiology, and field studies	80	1,180,000		60,000
7. Review and approval of grants	57	636,000		28,000
8. Program direction	25	230,000		7,000
C. Payments to the "National Institutes of Health management fund" for centrally furnished services:				
Laboratory and clinical research		3,984,000		391,000
Collaborative research and development		45,000		6,000
Biometry, epidemiology, and field studies		109,000		7,000
Review and approval of grants		722,000		95,000
Program direction		116,000		4,000
Total program increases			13	7,123,000
DECREASES				
A. 1 less day of pay in 1968 (total decreases)				−19,000
Total net changes requested			+13	+7,178,000

EXPLANATION OF CHANGES

Research grants.—The $3,930,000 increase will provide $3,181,000 for approximately 103 additional project grants and $749,000 for general research support grants.

Fellowships.—The increase of $567,000 will be used to support 5 research career development awardees ($264,000); 7 postdoctorals ($119,000); and 5 specials '$111,000). An increase for research career awards ($73,000) covers "cost-of-living" increases inherent in the program.

Training grants.—The increase of $148,000 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 $828,000 and 11 positions will provide for studies in the field of bacterial and mycotic diseases, and viral, mycoplasma, and rickettsial diseases.

Collaborative research and development.—The increase of $1,052,000 provides 1 position and $552,000 for the Vaccine Development Program and 1 position and $500,000 for the Transplantation Immunology Program.

Biometry, epidemiology, and field studies.—The increase of $60,000 provides for additional operating costs.

Review and approval of grants.—The increase of $28,000 provides for increased operating costs.

Program direction.—The $7,000 increase provides for increased operating costs.

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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 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 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

	1967 estimate	1968 estimate	Purpose
Comparative transfer to—			
"General research and services, National Institutes of Health".	—$3,000,000	0	U.S.-Japan cooperative medical science program.
"Other accounts"	—250,000	0	Redistribution of the National Institutes of Health management fund.
Transfer to "Operating expenses, Public Buildings Service," General Services Administration.	—12,000	0	Transfer of of rental costs to to GSA.

RESEARCH GRANTS

	1697 estimate	1968 estimate	Increase or decrease
Regular programs	$42,780,000	$45,961,000	+$3,181,000
Special programs	6,226,000	6,975,000	+749,000
Total research grants	49,006,000	52,936,000	+3,930,000

Introduction

In 1967, the Institute plans to support approximately 1,386 regular research projects in the amount of $42,780,000. The majority of these projects are on-

going noncompeting continuation grants which were approved for payment by advisory groups in 1966 and prior years for project periods of two to seven years. The noncompeting continuation grants represent 64% of the total regular research program.

It is planned to support 51 more competing awards in 1968 than are to be funded in 1967. The budget for both years reflects the policies which are in effect for arriving at the Federal and non-Federal share of research projects.

The Institute has developed a well organized mechanism, including its National Advisory Council and other advisory groups, that channel funds into specific areas of research by a system of priorities. These areas are continually redefined, and reviewed by the Institute staff and its advisory groups. The majority of the research grant funds are to be used for the support of ongoing and additional projects in free-ranging research related to the mission of the Institute. The highlights of the 1967 and 1968 program plans are as follows:

PROGRAM PLANS IN 1967 AND 1968

Allergy and other Immunologic Disorders

Transplantation Immunology.—In 1967, plans are to award approximately $3,207,000 for the support of research in this field. The Institute funds research projects in seven areas: tissue and cell typing, induction of tolerance in the adult animal, immunosuppression, enhancement, chemistry of transplantation antigens, immune events on the cellular level, and new assay systems of host-graft relationships. Monitoring of changes in the above emphasis areas is being continued by the Institute staff and expert consultants. In 1968 this program will amount to approximately $3,836,000, an increase of $629,000 over 1967.

Bacterial and Mycotic Diseases

Drug Resistant Bacteria.—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 $2,780,000 in 1967 and $3,250,000 in 1968, an increase of $470,000.

Leprosy.—Projects on cultivation of the leprosy bacillus, studies on animal transmission, development and evaluation of new anti-leprosy drugs and drug regimes, field trials of chromoprophylactic agents, and immunogenic agents are all considered feasible on the basis of present knowledge of the field.

Tuberculosis.—Emphasis will be placed on research on immunity and hypersensitivity in TB infection, leading to the development of a vaccine which is highly immunogenic but not allergenic. An increase of $99,000 is requested in 1968 over 1967.

Cholera.—Priority will be placed on programs for the development of an effective cholera vaccine which confers long-term immunity. Research must also be augmented on the treatment of cholera, its bacteriologic features and its pathogenesis, and on chemoprophylaxis of the infection.

Parasitic Diseases

Malaria.—Despite the immense research effort supported by this Institute and other agencies, several questions remain unresolved. The significant obstacles widespread chemotherapy of malarial infections brought about by the appearance in recent years of drug-resistant strains of human malaria is a vitally important problem. The Institute plans to award approximately $589,000 for work in this research area during 1967 with $677,000 projected for award in 1968, an increase of $88,000.

Schistosomiasis and filariasis.—Research will be developed on the biology and biochemistry of Schistosoma japonicum and its vectors, on comparisons of this species and other species that occur in different geographical regions, especially in relation to pathogenicity; and on immunology, pathology and chemotherapy and chemoprophylaxis of the disease. Similar efforts will be undertaken in the study of filariasis, especially the mechanism of action and pharmacology of anti-

filarial drugs. For both disease, research is needed on the cultivation of the parasites and on the physiology of the vectors.

Viral, Mycoplasma, and Rickettsial Diseases

Chronic and degenerative diseases.—Plans are to project a $2,200,000 program in the field of chronic and degenerative diseases of microbial origin during 1967. This area includes such dread diseases as chronic renal disease, multiple sclerosis, vascular disease, amyotrophic lateral sclerosis, connective tissue disease and emphysema. 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 to warrant fruitful participation in a broad-fronted attack on the problems of the infectious and immunologic genesis of the chronic and degenerative diseases in man.

The Institute plans to award approximately $4,300,000 in 1968, an increase of $2,000,000 over 1967, which will support and stimulate the growing interest in this field.

In recent years there has been an alarming increase in chronic-progressive respiratory diseases, often resulting in pulmonary emphysema. Additional support in 1966 for emphysema has permitted a definitive effort to explore the role of microbial agents and allergic comprehensive studies in large medical centers in which the various interrelating components can be intensively investigated and evaluated.

Infectious hepatitis.—It is estimated that $600,000 will be awarded for the study of infectious hepatitis during 1967 with $200,000 increase proposed in 1968. The importance of research on this disease is evidenced by the 1964 statistics of 745 deaths with 37,740 new cases reported. These figures are augmented by the long recovery period necessary and possibly permanent debilitating effects of this disease. Research in this area has been plagued by the problem of isolating etiological agents, and the equally great problem of establishing the significance of those agents which has been isolated.

Antiviral substances.—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 eventally be shown to be of viral orgin.

The great diversity of virus types necessitates the consideration of alternate approaches in combating viral diseases. Except for isolated instances, no generally useful drugs have appeared for the treatment of infections caused by the viruses.

Drug therapy in viral diseases must await the development of a rational approach to the synthesis of chemotherapeutic agents. This approach can 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 the structure and metabolism of nucleic acid and protein synthesis has produced a large resource base of interest and an opportunity for focus on antiviral activity in molecular biology. In this area it is planned to support projects amounting to approximately $3,500,000 in 1967, and $4,250,000 in 1968, an increase of $750,000.

Arboviruses.—Research will be concentrated upon two major areas: the arthropod-borne viruses (Japanese encephalitis, dengue viruses, Chikungunya, etc.) and the respiratory viruses, especially the influenza viruses. Research will be directed at strain differences, reservoir-host and reservoir-vector relationships, the imunologic studies leading to vaccine development, the effect of viral infection upon the central nervous system, etc. An increase of $86,000 is requested in 1968 over 1967.

The increased research activities mentioned above on leprosy, tuberculosis, cholera, schistosomiasis, filariasis and arboviruses are in support of diseases of interest to the U.S.-Japan Cooperative Medical Science Program.

Special programs

The increase of $749,000 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

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
1. Noncompeting projects	975	$27,404,000	1,027	$28,762,000	+52	+$1,358,000
2. Competing projects	405	14,376,000	456	16,199,000	+51	+1,823,000
3. Supplementals	(90)	1,000,000	(90)	1,000,000	0	0
4. Subtotal regular program	1,380	42,780,000	1,483	45,961,000	+103	+3,181,000
5. General research support		4,576,000		5,325,000		+749,000
6. Scientific evaluation		50,000		50,000		0
7. Gorgas Memorial Laboratory		500,000		500,000		0
8. Categorical clinical research centers	6	1,100,000	6	1,100,000	0	0
9. Total research grants	1,386	49,006,000	1,489	52,936,000	+103	+3,930,000

Research grants program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
Allergy and other immunologic disorders	$6,845,000	$7,374,000	+$529,000
Transplantation immunology [1]	(3,207,000)	(3,836,000)	(+629,000)
Bacterial and mycotic diseases	13,690,000	14,688,000	+998,000
Drug resistant bacteria	(2,780,000)	(3,250,000)	(+470,000)
Tuberculosis	(660,000)	(759,000)	(+99,000)
Parasitic diseases	5,133,000	5,515,000	+382,000
Malaria	(589,000)	(677,000)	(+88,000)
Viral, mycoplasma, and rickettsial diseases	17,112,000	18,384,000	+1,272,000
Chronic and degenerative diseases	(2,200,000)	(4,300,000)	(+2,100,000)
Infectious hepatitis	(600,000)	(800,000)	(+200,000)
Antiviral substances	(3,500,000)	(4,250,000)	(+750,000)
Arboviruses	(571,000)	(657,000)	(+86,000)
Subtotal regular program	42,780,000	45,961,000	+3,181,000
General research support grants	4,576,000	5,325,000	+749,000
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	49,006,000	52,936,000	+3,930,000

[1] Excludes $600,000 in categorical clinical research centers for 1967 and 1968.

NOTE.—Re "Increase or decrease" column—Nonadd items in the fields of allergy and other immunologic disorders and viral, mycoplasma, and rickettsial diseases show a greater amount than net program items due to reprograming within the fields.

FELLOWSHIPS

Total fellowships:	
1967 estimate	$3,700,000
1968 estimate	4,267,000
Increase or decrease	+567,000

Program plans in 1967 and 1968

The primary objective of the Fellowship Program is to increase the availability of trained professional researchers in allergy and infectious diseases.

The increase of $567,000 in 1968 will be used to support five additional Research Career Development Awardees, seven Postdoctorals, five Specials, and to cover the "cost-of-living" increases which are inherent factors of the ongoing Career Award Program.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	161	$2,647,000	169	$3,039,000	+8	+$392,000
(b) Competing	45	568,000	44	608,000	−1	+40,000
2. Supplementals	(7)	9,000	(7)	9,000	0	0
3. New	55	476,000	65	611,000	+10	+135,000
4. Total fellowships	261	3,700,000	278	4,267,000	+17	+567,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Postdoctoral	103	$706,000	101	$825,000	+7	+$119,000
2. Special	30	285,000	35	396,000	+5	+111,000
3. Research career:						
(a) Career	27	747,000	27	820,000	0	+73,000
(b) Development awards	101	1,962,000	106	2,226,000	+5	+264,000
4. Total fellowships	261	3,700,000	278	4,267,000	+17	+567,000

Training Grants

Total training grants:

1967 estimate	$9,103,000
1968 estimate	9,251,000
Increase or decrease	+148,000

The Graduate Training Grant Program provides the means to build more effectively for the future by supporting the research training of young scientists, particularly in neglected and rapidly expanding areas of prime concern. In some areas, such as immunology, virology and tropical medicine, notable progress is heavily dependent upon development of newly trained personnel. Program plans in 1967 and 1968 call for the continuation of training in the categorical areas of allergy, immunology, including transplantation immunology, infectious diseases, tropical medicine, parasitology and allied fields.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
a. Noncompeting	148	$7,350,000	140	$7,560,000	−8	+$210,000
b. Competing	21	1,296,000	21	1,361,000	0	+65,000
2. Supplementals	(5)	95,000	(5)	95,000	0	0
3. New	6	312,000	3	185,000	−3	−127,000
4. Scientific evaluation	(1)	50,000	(1)	50,000	0	0
5. Total training grants	175	9,103,000	164	9,251,000	−11	+148,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Graduate	175	$9,053,000	164	$9,201,000	−11	+$148,000
2. Scientific evaluation	(1)	50,000	(1)	50,000		0
3. Total training grants	175	9,103,000	164	9,251,000	−11	+148,000

Training grants program analysis

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Allergy and other immunologic disorders	47	$2,444,000	44	$2,484,000	−3	+$40,000
Bacterial and mycotic diseases	46	2,354,000	43	2,442,000	−3	+88,000
Parasitic diseases	25	1,267,000	23	1,288,000	−2	+21,000
Viral, mycoplasma, and rickettsial diseases	57	2,988,000	54	2,987,000	−3	+1,000
Scientific evaluation	(1)	50,000	(1)	50,000	0	0
Total training grants	175	9,103,000	164	9,251,000	−11	+148,000

LABORATORY AND CLINICAL RESEARCH

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	556	$5,184,000	567	$5,264,000	+11	+$80,000
Other expenses	--------	7,304,000	--------	8,482,000	--------	+1,178,000
Total	556	12,488,000	567	13,746,000	+11	+1,258,000

Introduction

The objectives of the intramural research program are the discovery and exploitation of new knowledge towards the goal of better prevention or treatment of those diseases of man caused by infectious agents or which result 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, protoza 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 still being discovered at frequent 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. The large number of still unsolved problems provide ample evidence of the need for a more vigorous multidisciplinary research effort which seeks 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 obligatory intracellular infectious agents (such as rickettsiae) which has become increasingly clear during the

past few years is that of persistence. New technics, developed in large part in the Laboratory of Infectious 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, endocrinological 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 chemotherapy or immunosuppression for cancer or organ transplant are other examples of what is becoming an increasing problem in medicine. Still more recently, the demonstration that several sarcoma viruses of animals exist in an 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 are opening 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 techonology 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, which enable it to take advantage of the geographic differences in prevalence of certain diseases, to work more safely with these diseases in their natural ecological habitats and in animal populations which cannot be accommodated at Bethesda, and to take advantage of certain human volunteer populations for the study of malaria. To these has been added the scientific responsibility for research in cholera under the State Department Agency for International Development (AID)—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 being coordinated under NIAID grant support by the U.S.-Japan Cooperative Medical Science Program with the SEATO Program are those related to isolation of the cholera toxin which causes the fatal diarrhea and the development of vaccines for neutralizing 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 will plan the translation of any apparent beneficial result to man whenever appropriate. Enlargement of the laboratory staff in East Pakistan with heavier demands for administrative and logistic support by the NIH plus the increased responsibilities involved in coordination of the U.S.-Japan Cooperative Medical Science Program in Cholera Research with the SEATO-Cholera Research Program will necessitate an increase in the number of NIAID personnel involved in these activities from five to a total of eight. It is hoped this can be achieved within existing resources in 1967 and 1968.

PROGRAM PLANS IN 1967 AND 1968

Allergy and other Immunologic Disorders

Allergic reactions now affect at least 20,000,000 Americans. Undesirable immunologic reactions block successful tissue transplantation, and chronic infections such as chronic bronchitis and pyelonephritis may have underlying immunologic disorders. These problems deserve a first-rate effort towards solution which is not readily achieved in grant supported research because of the necessity for long continued effort with a high possibility of failure.

The resignation of the former Clinical Director early in 1967 necessitated the recruitment of a new Clinical Director. Taking into consideration the unique facilities provided by the Clinical Center and the paucity in academic institutions of trained and active clinical investigators in the fields of allergy, clinical immunology and chronic infections, the decision was made to redirect the Labora-

tory of Clinical Investigations effort towards research in these problems by the recruitment of the new Clinical Director.

Chronic bronchitis and emphysema in particular will be a focus of effort because of the magnitude of the problem (in 1964 these were a primary cause of mortality in 20,000 deaths and a contributing factor in 41,000 others). This research program will be directed towards the discovery and elimination of causative factors, early detection and therapy, and rehabilitation.

This program will be achieved by reorientation in 1968 and when fully activated in succeeding years should provide a growing manpower pool for research on these difficult areas as clinical associates are trained and added to both the academic and governmental scientific community.

Bacterial and Mycotic Diseases

An increase of 1 position and $25,000 is requested for research on bacterial genetics directed toward discovering the evolutionary processes of the ever-increasing number of drug-resistant strains of bacteria. These strains render formerly effective antibiotics ineffective. Drug-resistant strain of staphylococcus threaten the success of many surgical procedures and is the scourge of many hospitals where they sometimes spread from patient to patient through routine hospital procedures. Tuberculosis is again emerging as a serious health problem due to the appearance of drug-resistant strains. The incidence of some bacterial diseases such as chronic pyelonephritis has not yielded to antibiotics. The Institute hopes to accumulate much basic information on how bacteria acquire drug resistance. Work on bacterial genetics has been pursued for many years but has been confined to only a few types of bacteria. The requested increase will enable the work to be expanded to other bacterial species.

Still another specific area of increased research activity during this period will be in the further development of a killed tuberculosis vaccine. Previous work has demonstrated that an extract of mechanically disrupted BCG cell walls in a mineral oil vehicle is capable of protecting mice from pulmonary challenge with virulent tubercle bacilli to a greater degree than living BCG vaccine. Further refinements and standardization have made possible the initiation of safety and protection tests in primates in cooperation with the National Primate Center at the University of California. Early results, while providing evidence of some protection, also revealed a number of problems that require solution before any real progress toward a vaccine for human use can be contemplated. Intensive efforts toward solution of these problems will require greater purification of the antigen, testing in large numbers of animals other than mice, and a more intensive bacteriological and pathological study of the test animals. Because of the importance of this effort to the U.S.-Japan Cooperative Medical Science Program on tuberculosis, some shifting of personnel and funds was accomplished in 1967 to enable extension of the work and there will probably be additional shifting of funds in 1968 to maintain the momentum.

Parasitic Diseases

The Institute will continue to explore the pathology of malaria in man and monkeys. Recent studies in the immunological and pathological aspects of malaria have confirmed that the host response to the presence of this parasite is extraordinarily complex. The nature of the immune response in malaria is so complicated by the involved life cycle of the parasite as to render the term immunity inappropriate in the usual sense. Simian models are now available in the laboratory to explore these basic and primary aspects of the host-parasite relationship. The availability of human volunteers in the long continued studies on chemoprophylaxis and chemotherapy for the more sophisticated aspects of the studies make the opportunities not only unique but imperative to pursue.

Research on filariasis and schistosomiasis will receive greater emphasis in the parasitic disease program in response to the demands of the U.S.-Japan Cooperative Medical Science Program. Filariasis research is concerned with the improvement of serologic tests for diagnostic purposes and with studies on the host-parasite relationship directed toward developing effective drugs for therapeutic and prophylactic use. Improved diagnostic tests and treatment techniques are also the major goals in the research on schistosomiasis. Studies in these areas will be intensified to discover effective preventive measures.

Viral, Mycoplasma, and Rickettsial Diseases

An increase of 5 positions and $150,000 is requested to embark on the investigation of viruses as a cause of some slowly progressing chronic diseases of presently unknown etiology of the nervous system, blood vessels, muscales, lungs, and kid-

neys of man. Some recent discoveries in one type of human neurological disease have pointed out the need for this important research. Investigators have conclusively shown that certain slowly developing fatal diseases of animals are caused by filterable agents. These diseases are characterized by unusual proliferative and degenerative processes which have a striking resemblance to disease processes occurring in etiologically obscure chronic diseases of man. Because mink, sheep, and goats are known to be susceptible to these animal viruses causing chronic diseases having similarities to some human diseases, the Institute proposes that they be tried as experimental hosts for the isolation of viruses from persons affected with certain chronic disease, utilizing the expanded animal facilities developed at Rocky Mountain Laboratory during 1967. Since long periods observation are necessary in studying diseases of this kind, incubation periods taking up to 2 years, it is necessary that a large number of animals be inoculated as soon as possible if any kind of definitive results are to be expected within 5 years. The animal work will be accompanied by intensified efforts to develop technics for isolation of these viruses in tissue cultures and to develop other diagnostic methodology.

An increase of 1 position and $55,000 is requested to bolster the research programs in hepatitis. Acute hepatitis is a major unsolved disease problem in the nation. The true incidence far exceeds the 50,000 cases reported each year because many cases escape recognition. Although a relatively mild disease in children, hepatitis in adults is serious and a high percentage of cases require more than a month of hospitalization followed by months of restricted activity. Research on this disease has been stymied because the infectious agent, believed to be a virus, has not been isolated. The requested increase would permit the Institute to develop and investigate several new technics which may make isolation of the hepatitis virus possible. Once this is done, the research logjam will break permitting possible vaccine development, early detection, and effective treatment of this disease.

An increase of 2 positions and $50,000 is requested to expand the work on antiviral substances, specifically to purify and identify the molecular structure of interferon. Interferon is a biological substance which is produced by cells a short time after they have been exposed to or infected by a virus and is probably involved in the primary mechanisms by which a hosts limits and cures virus infection. The progress which has been made in the war on viral diseases is limited to control of certain ones (e.g. poliomyelitis and smallpox) by vaccines. However, the great diversity of virus types (over 500 are known to infect man) dictate that the basic nature of virus infection and the body's reaction to it must be explored in order to find ways to effectively treat infections caused by viruses. Interferon is a promising lead in this exploration.

An increase of 2 positions and $150,000 is requested for the relocated and expanded long-term animal holding facility of the Laboratory of Infectious Diseases. This facility, located at the National Institutes of Health Animal Center, Poolesville, Maryland, was developed for long-term animal isolation and care in connection with studies on the oncogenic (tumor producing) properties of viruses. These studies are part of a program to define the cancer inducing properties of a large number of viruses which commonly infect man or animals in order to determine the viruses' importance as a possible cause of certain types of human cancer. Knowledge thus gained would be used to prevent the spread of potential oncogenic viruses through virus vaccines, a possibility that is a particular problem with adenoviruses and that presently hampers the further development of some very promising virus vaccines. The renovated facility will allow a marked increase in the number of animals which can be put to test and will permit an increase in the number of viruses with oncogenic properties under study. This increase will also allow the expansion of studies on the ability of these viruses to cause other late or obscure adverse effects on the host as these effects may relate to human chronic and degenerative diseases. The increases will provide adequate animal care and monitoring for the animals now under study. It will also permit procurement and maintenance of additional animals.

An increase of $398,000 is requested for the planned updating of laboratories in a program which will extend over several years. Most of the laboratory spaces occupied by the Institute were constructed 20 to 25 years ago and built-in laboratory benches, hoods, ventilation and exhaust systems, and even items of equipment are original in many areas.

Also included in this net increase is $39,000 for mandatory items such as annualization of positions new in 1967, and annualization of wage board pay increases in 1967, offset by one less day of pay in 1968. There are also increases

of $391,000 for centrally furnished services from the "National Institutes of Health management fund".

COLLABORATIVE RESEARCH AND DEVELOPMENT

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	33	$346,000	35	$362,000	+2	+$16,000
Other expenses		9,608,000		10,663,000		+1,055,000
Total	33	9,954,000	35	11,025,000	+2	+1,071,000

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) Virus Vaccine Development; and (3) Research Reference Reagents.

PROGRAM PLANS IN 1967 AND 1968

Allergy and other Immunologic Disorders

The overall mission of the *Transplantation and Immunology Program* is to achieve long-term success in human transplantation by intensive studies designed to develop successful histocompatibility typing methods, immunosuppressive therapy, and methods of organ preservation. An important primary goal is to determine the extent to which success in transplantation depends on histocompatibility (or tissue) typing. Tissue typing, if clearly correlated with graft acceptance, would then provide a sound scientific basis for organ transplantation. The first program goal was to produce certain reagents necessary before such a problem could be solved. During 1967, this goal was met and sufficient volumes of anti-leucocyte antisera for use in the matching of graft donors and recipients were produced. By the use of these reagents, rapid progress has been made in the determination of the total number of human transplantation antigens and it has been found that there are six or seven major tissue types rather than the twenty or so previously estimated. Recent studies by the Institute contractors show that with high quality reagents used by competent scientists, the relation between good histocompatibility typing and graft acceptance is excellent. Conversely, mis-matching and graft rejection are closely correlated. During 1967, intensive efforts are being made also to improve the technical aspects of tissue typing and the knowledge gained from these studies accounts for some of the recent successes in human transplantation.

During 1968 the program will be directed more toward evaluation of tissue typing in transplantation patients and less toward reagent production. The reagents already produced by the program will be used to solve the primary question of the value of histocompatibility typing. In the past, most of the poor results of typing could be blamed on either poor reagents or lack of technical competence in performance of typing tests. Further efforts to improve and standardize the quality of the program's reagents will be made. In addition, the Transplantation and Immunology Program will conduct courses for 10–12 scientists per course in modern techniques of histocompatibility typing. These courses will be taught by selected member of our advisory committee and contractors. Courses of this type are essential if scientific competence in this field is to be increased in the United States.

There is a need to conduct tissue typing evaluation studies where the typing of recipient and donor can be done prior to transplantation. It is now thought by most scientists that transplantation is feasible with typed cadaver organs. Due to the large number of recipients that must be typed to match a single donor, studies of this type can currently be done only in large metropolitan areas. The Transplantation and Immunology Program in the transplantation evaluation centers will be closely correlated and integrated with existing dialysis and surgical programs. During 1968, several transplantation evaluation studies will be initiated in the United States.

Some of the funds requested for 1968 will also be used to support studies on the preservation of organs, particularly the kidney. Although certain tissues can now be preserved by freezing (corneas, heart valves, tissue cultures, etc.) freezing whole organs has not been successful and preservation by other techniques have so far been limited to a few hours. One of the greatest obstacles to a fully effective transplantation program is the availability of viable and functional organs. A system for preserving such organs for several days would allow sufficient time for typing, matching and transportation to a recipient anywhere in the country.

Further studies are planned to relate the degree of success in tissue typing to various problems in clinical management, particularly in relation to dosage levels of immunosuppressive drugs needed when donors and recipients show various degrees of histocompatibility matching.

An increase of 1 position and $500,000 is requested in 1968 over 1967.

Viral, Mycoplasma, and Rickettsial Diseases

During 1967, 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. Certain high-risk population groups including infants, children, and the aged are particularly affected by these respiratory agents.

The rubella virus is recognized as an important cause of congenital defects, including mental retardation in children born to mothers contracting German measles in early pregnancy. Every effort is being directed toward the development of a safe and effective vaccine to prevent the occurrence of German measles. An attenuated strain of rubella virus has been developed by investigators at the Division of Biologics Standards. Work on this strain and other strains suitable for vaccine purposes will be expanded. The program is supporting thirteen contracts for research, development, and testing of prototype rubella vaccines. It will be necessary to test a number of different strains in order to select that strain which best meets all the criteria for a safe and effective vaccine. These criteria include the following requirements: inability to induce clinical illness and viremia; non-transmissability of the vaccine virus from vaccine 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 lifelong immunity to the natural disease; and ability of the vaccine strain to grow to high titer in a cell culture system acceptable for administration eventually to millions of children. The program has developed and standardized diagnostic reagents and methodology necessary for the laboratory evaluation of vaccines. Work on an inactivated vaccine will be continued, particularly because of the need for a preparation of this type in women of the child-bearing age.

In 1967, respiratory virus vaccine development is continuing at a high level of productivity. Institute scientists, collaborating with the pharmaceutical industry and with Army and Navy scientists, have developed a vaccine that is protective against adenovirus type 4 infection, the most important cause of respiratory disease in the military. Field trials in 50,000 recruits have been eminently successful. The vaccine is at least 95% effective and there have been no untoward effects. In order to satisfy a national defense need, 750,000 tablets of the vaccine have been made available this year to the military. An experimental vaccine for the important group of pneumonias caused by a pleuro-pneumonia-like organism has been developed and has been shown to be moderately effective. Several improved mycoplasma vaccines are now being produced and clinical trials will be initiated shortly. Experimental respiratory syncytial and parainfluenza vaccines have been developed and have under-gone clinical trials in young children, the group most susceptible to the severe illnesses produced by natural infection.

Results have shown the parainfluenza vaccines to be effective. A trivalent parainfluenza vaccine (combining types 1, 2, and 3) has been produced, and combinations made with still other vaccines. The potential of certain respiratory viruses to cause tumor formation in experimental animals continues to require an intensive effort to prevent the use of oncogenically contaminated virus strains.

In 1968, there will be increased procurement and testing of experimental lots of vaccines for clinical trials. Work on the preparation of vaccines for the rhinoviruses which are the main causative agent of the common cold will be increased.

An increase of 1 position and $552,000 is requested in 1968 over 1967.

In 1967, the *Reference Reagents Program* has emphasized (1) completion of reference reagents production for those accepted viral prototypes of the adeno, myxo, entero, and herpes virus groups; (2) continued production, testing and certification of both type specific and grouping reagents for arboviruses; (3) continuation of the production, testing and certification of human and animal mycoplasma reagents in a cooperative effort with Division of Biologics Standards; (4) planning and initiating rhinovirus reagent production, testing and certification; and (5) pilot studies on the methodology for improved ampuling, packaging, and storing of labile reference reagents.

In 1968, primary emphasis will be on (1) facilitating and expediting production of vitally needed rhinovirus and arbovirus reference reagents; (2) conducting an intensive research and development program an lyophilization and storage of reference reagents; (3) re-examining research reference reagents produced under previous contracts now in the repository to determine viability, titers, etc., and presence of contaminants now detectable by methods not previously available, and planning and initiating production of replacement reagents where indicated; (4) studying and developing 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; and (5) planning, developing, and initiating production of reagents to those additional organisms causing infectious and parasitic disease, in response to needs for other standardized microbial reagents not commercially available.

Included in this net increase is $13,000 for annualization of positions new in 1967 offset by one less day of pay in 1968. There is also an increase of $6,000 for services furnished centrally by the National Institutes of Health management fund.

Biometry, Epidemiology, and Field Studies

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	80	$603,000	80	$603,000	0	0
Other expenses	--------	686,000	--------	753,000	--------	+$67,000
Total	80	1,289,000	80	1,356,000	0	+67,000

Biometry, Epidemiology, and Field Studies are primarily related to insect transmitted virus diseases as represented by the Middle America Research Unit in the Panma Canal Zone, and the arbovirus research program at the Rocky Mountain Laboratory. These activities have also been identified as important ingredients in the U.S. element of the U.S.-Japan Cooperative Medical Science Program of arbovirus research and provide support in the form of project officers to the Reference Reagents Program of the Institute. Other epidemiology and field studies relate to respiratory diseases in an institutional population where new causative agents are being sought and to studies on certain fungus and leptospiral infections in Panama.

Of the net increase, $60,000 is requested to take care of the increased costs of maintaining current levels of support for operating costs and $7,000 for centrally furnished services from the National Institutes of Health management fund.

REVIEW OF APPROVAL OF GRANTS

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	57	$565,000	57	$565,000	0	0
Other expenses		793,000		917,000		+$124,000
Total	57	1,358,000		1,482,000	0	+124,000

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 $28,000 will provide for increased operating costs. Included in the net increase requested is $1,000 for annualization of a position new in 1967, offset by one less day of pay in 1968. There is also an increase of $95,000 for centrally furnished services from the National Institutes of Health management fund.

PROGRAM DIRECTION

	1967, estimate		1968, estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	25	$241,000	25	$241,000	0	0
Other expenses		105,000		118,000		+$13,000
Total	25	346,000	25	359,000	0	+13,000

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 $7,000 will provide for increased operating costs. Included in this net increase is $2,000 for annualization of a position new in 1967, offset by one less day of pay in 1968. There is also an increase of $4,000 for centrally furnished services from the National Institutes of Health management fund.

New positions requested, fiscal year 1968

	Grade	Annual salary
Laboratory and clinical research:		
Medical officer	GS-13	$15,561
Do	GS-12	13,201
Chemist	GS-11	9,536
Do	GS-7	7,729
Biological laboratory technician (3)	GS-7	19,353
Do	GS-5	15,993
Surgeon	Full	9,644
Total (11)		91,017
Collaborative research and development:		
Medical officer	GS-13	15,561
Secretary	GS-5	5,331
Total (2)		20,892
Total new positions, all activities (13)		111,909

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

LIST OF WITNESSES

DR. FREDERICK L. STONE, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

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

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. WILLIAM H. STEWART, SURGEON GENERAL

G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER

JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	1,400	1,903	2,084
11.3	Positions other than permanent	45	42	42
11.5	Other personnel compensation	20	32	32
	Total personnel compensation	1,465	1,977	2,158
12.0	Personnel benefits	123	190	214
21.0	Travel and transportation of persons	124	146	193
22.0	Transportation of things	4	18	23
23.0	Rent, communications, and utilities	79	112	152
24.0	Printing and reproduction	9	19	24
25.1	Other services	73	97	115
	Projects contracts	3,196	3,393	3,506
25.3	Payment to "National Institutes of Health management fund"	1,543	1,654	1,879
26.0	Supplies and materials	29	57	58
31.0	Equipment	66	61	60
41.0	Grants, subsidies, and contributions	121,246	138,307	151,902
99.0	Total obligations	127,957	146,031	160,284

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	181	209	221
Full-time equivalent of other positions	5	4	4
Average number of all employees	161	199	215
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	61,429	75,172	85,263
(b) Fellowships	18,442	19,400	20,910
(c) Training	41,375	43,735	45,729
Total, grants	121,246	138,307	151,902
2. Direct operations:			
(a) Collaborative research and development	514	3,231	3,448
(b) Training	97	295	484
(c) Review and approval of grants	2,325	2,784	3,023
(d) Program direction	1,048	1,226	1,328
Total, direct operations	3,984	7,536	8,283
Total program costs, funded [1]	125,230	145,843	160,185
Change in selected resources [2]	2,727	188	99
10 Total obligations	127,957	146,031	160,284
Financing:			
16 Comparative transfer from other accounts	−895	−968	
25 Unobligated balance lapsing	124	25	
New obligational authority	127,186	145,088	160,284
New obligational authority:			
40 Appropriation	127,188	145,113	160,284
41 Transferred to—			
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−2		
"Operating expenses, Public Buildings Service," General Services Administration (80 Stat. 674)		−25	
43 Appropriation (adjusted)	127,186	145,088	160,284
Relation of obligations to expenditures:			
10 Total obligations	127,957	146,031	160,284
70 Receipts and other offsets (items 11–17)	−895	−968	
71 Obligations affecting expenditures	127,062	145,063	160,284
72 Obligated balance, start of year		94,967	114,551
74 Obligated balance, end of year	−94,967	−114,551	−144,802
90 Expenditures	32,095	125,479	130,033

[1] Includes capital outlay as follows: 1966, $36,000; 1967, $79,000; and 1968, $60,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $0; 1966, $2,727,000; 1967, $2,915,000; 1968, $3,014,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Name: Frederick L. Stone.
Position: Director, National Institute of General Medical Sciences.
Birthplace and date: Biloxi, Mississippi; March 31, 1915.
Education: 1937, Middlebury College, Middlebury, Vermont (Chemistry), B. S.; 1942, University of Rochester, Rochester, N.Y. (Biology), M.S.; 1948, University of Rochester, Rochester, N.Y. (Biology), Ph. D.; 1949–53, American University, Washington, D.C. (Public Administration).
Experience: August 1964 to present, Director, National Institute of General Medical Sciences, National Health Institutes of Health; July 1962 to August 1964, Chief, Division of Research Facilities and Resources, NIH; January to July 1962, Acting Chief, Division of General Medical Sciences, NIH; 1958–1962, Assistant Chief, Division of General Medical Sciences, and Chief, Research Training Branch, DGMS, NIH; 1957–1958, Assistant Chief, Division of

Research Grants, and Chief, Research Training Branch, DRG, NIH; 1956–1957, Assistant to the Associate Director, NIH; 1955–1956, Director, Medical and Scientific Department, National Multiple Sclerosis Society, New York; 1954–1955, Assistant for Professional Services to the Vice-Chancellor, Schools of the Health Professions, University of Pittsburgh, Pittsburgh, Pa.; 1951–1954, Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, NIH; 1948–1951, Chief, Research Fellowships Branch, Division of Research Grants, NIH; 1947–1948, Instructor in Biology, University of Rochester, Rochester, N.Y.

Association memberships: American Association of Medical Colleges; American Association for the Advancement of Science; American Academy of Neurology; American Society of Ichthyology and Herpetology; American Historical Society (ISIS); Association for Research in Nervous and Mental Diseases; Association for Research in Ophthalmology; Cosmos Club, Washington, D.C.; Sigma Xi; the Royal Society of Medicine (Affiliate).

Special awards and citations: 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. Our next witness is Dr. Frederick L. Stone, Director of the National Institute of General Medical Sciences. Dr. Stone, would you proceed with your statement?

GENERAL STATEMENT

Dr. STONE. Mr. Chairman and members of the committee, it is a privilege to appear before you on behalf of the National Institute of General Medical Sciences in connection with the appropriations for fiscal year 1968.

I welcome especially the opportunity to tell the new members of this committee something about this Institute, its development, major areas of emphasis, and its key activities.

RATIONALE FOR INSTITUTE FOR GENERAL MEDICAL SCIENCES

Most of the National Institutes of Health's categorical or, as they are sometimes called, disease-oriented, Institutes were established in the late 1940's or early 1950's. Despite the need for a fundamental scientific underpinning for the more practical activities in each Institute, it was soon evident that a more general organization was needed to assure stable growth for a number of scientific areas such as biochemistry, pharmacology, genetics, and biophysics, which, though essential to the growth of each of the categorical programs, are general in nature and therefore could not be expected to flourish without some central point of scrutiny and support.

It was the need for such a central concern that resulted in the development of the National Institute of General Medical Sciences. Very early it became apparent that certain general clinical areas, for example, anesthesiology and surgery, which are important to many of the categorical programs, could also profit by being the responsibility of such a central operation.

Basic information in these areas is essential to the categorical Institutes because, concentrating as they must on areas of the basic science directly related to specific diseases, they cannot provide the undifferentiated base for an as yet undiscernible application.

Grants to support this type of research were, for the first 10 to 12 years of the modern development of the National Institutes of Health, assigned to one of its administrative units, the Division of Research Grants and, later, in 1958, to a new division, the Division of General Medical Sciences, the forerunner of the present Institute.

TRAINING GRANTS AND FELLOWSHIPS

Early in the development of the latter Division it was assigned the responsibility for administering the bulk of the National Institutes of Health training programs supporting youth health scientists working for advanced degrees. These programs result from the effective use of two administrative mechanisms: the training grant and the fellowship.

The training grant to a medical school or other institution supports and enriches the research environment and introduces the beginning researcher to broad perspectives of research under experienced and highly competent teachers. The fellowship, on the other hand, enables individuals of competence and potential, in whatever institution or locality, to advance in their scientific field.

In a more general view, as the concept of the Division of General Medical Sciences became established, it grew in both size and importance. Congress raised the Division to Institute status in 1962, and so, by law, stabilized a series of functions which had been shown to be essential in the administration of the broad programs of the National Institutes of Health.

SUPPORT OF NEW FIELDS

The Institute has been alert to new scientific developments and has made necessary adjustments to provide adequate balance and coverage to a number of related fields of science, and has supported the development of new fields such as biophysics and biomedical engineering as the needs for these disciplines were perceived to be important.

BEHAVIORAL SCIENCES

An excellent current example is the Institute's operation in its recent assessment of the need for an expanding role for the behavioral sciences as an essential part of the developing biomedical sciences. An assessment of the total behavioral science requirements for the National Institutes of Health has been completed and a determination of the specific role of this Institute in such a development is now in progress.

AUTOMATION OF CLINICAL LABORATORIES

A more specific program development that can be noted, for purposes of clarifying the function of this Institute, is its current support of studies on the automation of clinical laboratories.

The number of tests performed in the average hospital laboratory has increased exponentially in the past few years. Until recently, a

fairly small number of routine tests were performed on blood and other body constituents. Now, however, dozens of tests using complicated techniques and highly specialized instruments are routinely carried out for diagnosing coronary heart disease, endocrine malfunction, and various metabolic disorders. Not only has the complexity of laboratory tests increased, but also the number of tests for each patient admitted to a hospital. Instead of an average of three or four tests for a patient, batteries of tests are required.

The situation has reached a critical point. Patients cannot always get, either in quantity or quality, the diagnostic tests they need. In many hospitals, laboratory methods are crude, even antiquated. And there are by no means enough technicians and professional laboratory workers to cope with the vastly expanded workload.

In April 1966, the Institute of General Medical Sciences sponsored a conference of experts in clinical research, mass medical screening, automation, computer technology, and other fields related to the subject of automation of clinical laboratories.

Following that meeting, the Institute took steps to increase the program it was already supporting in various aspects of clinical laboratory automation. Among those projects is the work of Dr. Donald Glaser, a Nobel Prize winner at the University of California at Berkeley, who is working on automated diagnostic procedures in bacteriology. Using computers, these studies make possible rapid identification of bacteria in, for example, infected wounds or blood poisoning. Dr. George Brecher, of the University of California Medical School in San Francisco, is developing computer-controlled instruments and data collection systems for clinical chemistry and hematology.

The Institute has several grants and contracts for projects in the development of automated analytical instruments that can perform multiple tests dependably, rapidly, and possibly more economically. These tools become even more effective when combined with computer systems for analyzing and reporting results.

Though automation can alleviate some of the tremendous workload in clinical laboratories, it cannot yet solve some of the problems caused by the large number of requests for sophisticated, special tests developed at the research level which so far have not seemed adaptable to automation. The Institute is supporting research that ultimately could result in the automation of some of these more chemically demanding tests.

As part of its program development in clinical laboratory automation, the Institute this past February named Dr. Thomas D. Kinney, who is chairman of the department of pathology at Duke University, principal consultant to assist in the development of this research support program. Dr. Kinney, who will spend a year with the Institute, was chairman of the conference held in April 1966 at which the problems in clinical laboratory automation were discussed and recommendations made for their solution.

BIOMEDICAL ENGINEERING

Among the emerging scientific disciplines supported by the Institute is biomedical engineering—a new area of science that brings together the physical sciences (represented by the engineer) and the

medical sciences (represented by the physician) and draws upon the knowledge of both for support.

Electrical engineers working with physicians and scientists at Case Institute of Technology in Ohio are studying methods for restoring activities of muscles and nerves damaged by disease or accident by implanting in muscles and tissues electronic devices smaller than an aspirin tablet.

Dr. Wen H. Ko and his Case Institute associates are designing, developing, and perfecting these extremely small electronic implant systems to monitor heartbeats, blood pressure, and body temperature in studies of disease. Microelectronic devices that could be implanted to control the activity of parts of the body including the heart, bladder, and nervous system would be of enormous benefit to victims of stroke and other disabilities. Dr. Ko and his fellow scientists have already used an implanted electronic device to stimulate repeated leg movement in rabbits, laboratory evidence of the possibility of a major advance toward ultimately rehabilitating paralytics through electronics.

PHARMACOLOGY-TOXICOLOGY PROGRAM

The National Institute of General Medical Sciences also emphasizes its pharmacology-toxicology program, a coordinated national effort to study the effects of drugs on biological systems with the major objective the improvement of the efficacy of drugs and their safety.

In this program, the Institute employs all its research support mechanisms—grants for research projects, training, and fellowships and contracts as well as special funds for center development—to study drug action at the cellular level, and, finally, the effect of drugs in human beings. This program also embraces toxicology as well since information on the toxic effect of a drug used in the treatment of a disease may be as important as the knowledge of its therapeutic effect. Drug safety is an essential and integral aspect of the entire program.

At the University of Iowa, where the Institute supports one of its three pharmacology-toxicology centers, scientists are attempting to refine their methods for evaluating drug toxicity by inducing what are called model disease states in laboratory animals, that is, diseases similar to those found in man that can be used in research with greatly improved specificity.

So far, the scientists have induced renal disease, neurogenic disease, and endocrine disorders in several animal species. Eventually, they will be able to relate findings from these studies to similar drug studies in man. This work at Iowa is a significant example of how Institute-supported pharmacology-toxicology research is moving in new directions.

ANESTHESIOLOGY

In 1965, Dr. Michael DeBakey, nationally known heart surgeon; Dr. E. M. Papper, one of the Nation's leading research scientists in anesthesiology; and other leading surgeons and anesthesiologists met at a conference sponsored by this Institute in Philadelphia to discuss the manpower crisis in anesthesiology.

From that meeting emerged a vastly stepped-up Institute-supported program in anesthesiology, which, with Dr. Papper as principal consultant for 6 months, has grown steadily in scientific importance.

Testimony to this growth is reflected in the increase from $1,334,000 for research grants and $404,000 for research training grants in anesthesiology in 1966 to the estimated $2 million for research grants and $2,042,000 for research training grants to be awarded for that purpose in 1967, an overall increase of $666,000 in research grants and $1,638,000 in research training grants.

Because the metabolism and full range of action of anesthetics is not fully understood, they are, perhaps, not always administered as effectively and safely as they should be. Such basic knowledge should be available to the anesthesiologists and to other physicians as well.

The development of improved instrumentation and of manpower trained in its use also is important to anesthesiology.

Today, three anesthetists often are required to attend a single patient during complex operations such as those required in open chest surgery. Scientists are working on the refinement of computers which continuously monitor physiological processes and advise of changes in the state of the patient. Ultimately, some of these computers may help compensate for the critical shortage in certain categories of trained technical personnel.

Another aspect of the Institute's program in anesthesiology was its support of a 3-year study of the safety of the anesthetic halothane which had been linked with fatal liver damage. The study showed halothane to be as safe or safer than other general anesthetic agents on the basis of postoperative mortality. The study also established that the massive fatal liver damage following administration of halothane or other anesthetics in surgery is rare and not significantly associated with any single anesthetic practice, as previously had been suspected.

In the past year the Institute inaugurated a new program for the support of residents in anesthesiology. The $1 million appropriated by the Congress for this program will enable the Institute to make approximately 15 awards by the end of the fiscal year. Congress has also provided funds for the establishment of centers for research in anesthesiology and diagnostic radiology and several applications are now under review.

GENETICS

The anesthesiology program is one whose benefits to patients are obvious. The relation of genetics to disease, however, may not be so obvious, but it is of utmost importance. Some 500 diseases and disabilities have been linked to genetic factors, an indication of the extensive role genetics plays in disease.

The entire field of genetics, from molecules to chromosomes to man, and to whole populations, is one of the most promising in the unending effort to improve man's health.

Understanding the mechanisms of hereditary diseases requires knowledge of the detailed chemical architecture of all molecular components of the hereditary process, a field of scientific endeavor called genetic chemistry.

To explain the chemical structure of genetic material, the Institute also has a collaborative research project with Oak Ridge National Laboratory to study methods for separating protein molecules and for developing new methods of producing the biological materials

needed for genetics research. Scientists on this research project have devised novel techniques for isolating a few kinds of pure genetic materials (s-RNA) and have produced more pure material of this kind than ever has been produced before for research purposes.

Genetic abnormalities are sometimes revealed by abnormal numbers of chromosomes in body cells, but the slow process of counting chromosomes has been a hindrance to genetics research.

The Institute supports a project that not only speeds chromosome counting but gathers and analyzes other data more rapidly.

Investigators in this project are developing a device that automatically scans photographs and, aided by a computer, analyzes quantitatively the information on the photograph. A special technique emphasizing fine details will be used to obtain data from pictures of chromosomes, neurons, and other materials.

Clinical genetics, a rapidly developing field, is so new that only 10 years ago, in 1956, were techniques developed which enabled scientists to determine accurately that 46 is the normal number of cromosomes in each cell in man.

I might say some years ago, before Senator Hill, I was acutely embarrassed by telling him 48 was the number which it had been for 30 years. Some idea of the significance of this figure is illustrated by the fact that children suffering from mongolism, or Down's syndrome, have 47 choromosomes instead of the normal 46. The relation of chromosomal abnormality to mental retardation has been definitely established and certain types of aberrant behavior have been linked to chromosomal abnormalities.

TRAINING PROGRAMS

The development of a strong base in biomedical research requires ready availability of highly trained manpower to develop new techniques, to investigate new approaches, and to apply basic information to the study of disease. To this end, the Institute supports most of the Nation's training in the basic medical sciences.

The single most important element of any training program is the young man or woman who enters graduate school or medical school and works toward the doctoral degree. The Institute now support some 5,000 predoctoral students in training. The complexity of science and the new scientific areas developing so rapidly make it essential for most doctoral graduates, whether with an M.D. or a Ph. D., to take postdoctoral training for a year or more to develop scientific competence in greater depth. Even established scientists find that from time to time they must take additional intensive training in new techniques and in the use of new types of equipment. The Institute, therefore, supports a large program in postdoctoral and special fellowships, the latter being awarded in the main to established scientists for special, advanced training.

Typical of such fellowship recipients supported by this Institute is a 27-year-old doctor of medicine who received his bachelor of science degree from the Massachusetts Institute of Technology in 1961, and his doctor of medicine degree in 1965 at the University of Pennsylvania. As a research assistant under the joint auspices of MIT and Boston University Medical Center, he participated in the application

of computer technology to the patient-care phase of hospital operation. He joined the Massachusetts General Hospital staff to work on the development of a comprehensive hospital information system under a grant with this Institute.

We support a small but significant program of training grants in the postdoctoral area involving the clinical sciences of anesthesiology, surgery, and diagnostic radiology together with clinical pharmacology and biomedical engineering. Here most of the fellows-in-training enter the program with the M.D. degree and spend their 3 to 5 postdoctoral years in obtaining a high competence in one of the basic sciences directly related to their research efforts—in special programs designed to improve clinical care through the application of new techniques developed from basic medical research.

I should like to reemphasize briefly, as examples, the three broad, scientific areas of pharmacology and toxicology, genetics, and anesthesiology which among many supported by the National Institute of General Medical Sciences are committed to improving the Nation's health.

The pharmacology-toxicology research supported by this Institute demonstrates how an organized program is beginning to blend equipment, facilities, and the Nation's pharmacological and pharmaceutical talent in an effort to improve the safety and efficacy of drugs.

Anesthesiology touches the lives of millions of Americans—in surgery, treatment of accident victims, in respiratory problems, and in countless other situations.

Institute-supported programs in genetics which I merely touched upon, emphasize basic knowledge and its possible application to specific diseases and handicaps.

Mr. Chairman, the appropriation request for the National Institute of General Medical Sciences for 1968 totals $160,284,000, an increase of $14,253,000 over the comparable figure for 1967. Of the total amount requested, $85,263,000 is for research grants; $20,910,000 for fellowships; $45,729,000 for training grants; $3,547,000 for collaborative research and development; $484,000 for training activities; $3,023,000 for the review and approval of grant applications; and $1,328,000 for program direction.

I shall be very happy to answer any questions or provide additional information.

SUMMARY OF BUDGET REQUEST FOR GENERAL MEDICAL SCIENCES

Mr. FLOOD. Thank you, Dr. Stone, for an excellent presentation.

The adjusted appropriation, Doctor, for 1967, is $146,056,000. The request for 1968 is $160,284,000. That is an increase of $14,228,000.

Now, a little bit over $10 million is for research grants. As Rudyard Kipling said of the Irish guards, "You are pretty new at this game." Yours is a pretty new institute compared to others. Most of this is to finance projects which were started last year and this year that will continue into 1968.

As a matter of fact, you aren't going to be able to finance as many new projects in 1968 as in 1967, are you?

Dr. STONE. Well, sir, ours is the newest institute as a technical, legal entity, but we are by far the oldest program of grant support of the NIH.

Mr. FLOOD. Let me finish the Kipling quote.

He said:

> 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 have to be Irish to understand that, but I think that is about what your position is, even though you are a "new" institute.

CONTINUATION PROJECTS

Dr. STONE. Of the $10,091,000 rise requested in research grants, we feel that the sums might be used in support of regular projects; about $6,928,000 could be used for this purpose, and it is our plan, if the money is granted, to so proceed.

Mr. FLOOD. New projects?

Dr. STONE. These are noncompeting continuations, sir. They are not new projects in the sense of never having been supported. They are continuation projects.

Mr. FLOOD. Yes, that is the point I made a minute ago.

COMPETING PROJECTS

Dr. STONE. That is correct, sir. We would intend to use for strictly competing projects—that would be brandnew projects in certain cases—about $700,000. We expect, on the basis of experience extending over the years, that we would pay about $318,000 to $320,000 in supplementals. This is based on our experience over the years.

We plan to put an additional $500,000 into anesthesiology and diagnostic radiological research. This has been approved by the Bureau of the Budget.

LOW BUDGET PRIORITY FOR GENERAL MEDICAL SCIENCES

Mr. FLOOD. As I recall it you had quite a problem selling Congress, and even a lot of doctors, on the importance of basic research in this whole field of biophysics, microbiology, and so forth. Finally you did sell it, and you got everybody all steamed up about this thing. Then for no apparent reason, instead of following through on all this enthusiasm, you are starting to cut back. That isn't an unfair statement, is it?

Dr. STONE. It is not within my power and authority to set the limits and I am assuming those above me have difficulty in deciding upon competing and mutually exclusive requests for funds. The funds which have been provided here of more than $10 million are the funds they felt could be added and requested during the fiscal year 1968. These funds represent what the Chief Executive thought could be wisely spent. The Chief Executive is clearly aware they represent something less than half of the scientifically approved requests which we have waiting to be awarded.

Dr. SHANNON. We gave this appropriation special consideration in the allowances, and in our support for these programs because we feel that it is truly one of the key areas in the total program.

Mr. FLOOD. Yes, you were the chief salesman. I feel the same about these activities now as I did then.

Dr. SHANNON. This really plays a key role in the development of total programs in much the same way as do the research centers in the application of knowledge that I spoke about earlier. These are two areas that are at the heart of progress in the total programs. One on a broad, fundamental, underpinning level; the other in terms of the direct application of knowledge. I think any curtailment of these programs would indeed have repercussions in all the categorical areas.

I point out certain areas, behavioral sciences, biomedical engineering; the heavy programing is going on in anesthesiology, in certain research aspects of surgery, areas of trauma that I mentioned yesterday which we associate with head injury programs. It makes up a combination of activities which mutually reinforce one another in a highly effective way and the basic needs of this Institute led us to give it preferential treatment when the final dollar ceiling was set.

Mr. FLOOD. I agree with you and I believe you did give this Institute priority, but it certainly has lost momentum.

TRAINING GRANTS

For instance, you show a decrease of 18 in the number of training grants you will be able to finance next year. What about that, Doctor?

Dr. SHANNON. I was very unhappy about that, Mr. Chairman.

Mr. FLOOD. Are you equally unhappy?

Dr. STONE. Yes, sir.

Dr. SHANNON. I must point out that this is not because it was not given very high priority within the National Institutes of Health. It was also given high priority in the Public Health Service and high priority in the Department. This was one of two areas for which we emphasized the essentiality of moving forward in training, but the decision was made—for, I am sure, very good reasons—that training, across the board, would be held at much the same level.

In this particular appropriation, although the request by the Department to the Bureau of the Budget was for $49.3 million for training, Dr. Stone is only able to approach you with a figure of $45.7 million. I think that the support for this appropriation at all levels within the executive branch—except in the final determination of how much money could be made available—would attest to the essentiality of this appropriation.

MANPOWER PROVISIONS IN THE BUDGET

Mr. FLOOD. You have a decrease of 126 in fellowships.

Gentlemen, I have heard all these statements that we don't have doctors, we don't have dentists, we don't have technicians, we don't have laboratory technicians, we don't have this and we don't have that; we can't do this because we can't get the faculty. But then all I have seen here, institute after institute, is cut backs on training grants, cut backs on fellowships. How in the world do you put this together?

Dr. SHANNON. We can only say that when the final decision had to be made, within a budget ceiling either to support already-established scientists or to train, we elected to support those already trained.

Mr. FLOOD. Are you suggesting you have a lot of scientists stored away in a closet somewhere that you could put to work if you had money? Surplus scientists.

Dr. SHANNON. I would say that Dr. Stone's Institute will probably only pay half the approved research grants that come before his council.

Dr. STONE. A quarter.

Dr. SHANNON. A half this year, a quarter next year. There are many scientists who will not be supported by appropriations at these levels.

Mr. KELLY. A high degree of emphasis has been given manpower. In prior years a very substantial increase in the development of professional manpower in research and scientific areas occurred.

The budget for this fiscal year is an expansion in the development of professional manpower, the creation and support of new medical schools, the expansion of enrollment in medical and dental and health-related schools. We will find the health budget puts a tremendous emphasis in the area of professional manpower, but it does not reflect itself in a substantial expansion in the development of the postdoctoral research in the manpower area.

Mr. FLOOD. That is mostly fellowships you are speaking of.

Mr. KELLY. That is right.

Mr. FLOOD. What about training?

Mr. KELLY. The emphasis we find in the budget this year is really the development of the service capability in the health profession—new and expanded medical schools, dental schools, and similar activities.

DIRECT OPERATIONS

Mr. FLOOD. Now, as are all the other Institutes, you are asking for an increase for direct operations. You want to finance 12 new positions. What will happen if you don't get the 12?

Dr. STONE. What will happen if we don't get the 12 is that we will be put in fairly bad shape as follows: First of all, we are a small Institute and 10 of the 12 positions are requested for what I will call Fellows-in-training in the intramural program. At the National Institutes of Health, we have perhaps certainly one of the world's great centers in the pharmacology. It was decided a couple of years ago to request money for 10 additional fellows each in 3 years, making a total of 30 at the end of 1968 if the funds are granted. These Fellows will leave the National Institute of Health with some of the best training in the field of pharmacology that is available today. Ten of those 12 are Fellow-in-training. They would come and be trained and would in some small measure offset the manpower deficit that you have been talking about.

Two only, of the additional people, are actually on my operating staff.

Dr. SHANNON. Mr. Chairman, this item of 10 positions for people to be trained at NIH through fellowships reflects a policy decision to push our own resources to the limit. I would go further than Dr. Stone, who said that we have one of the better scientific establishments in this particular area. Beyond any doubt, we have the highest concentration of very top-flight people.

After discussing this with many people in the universities, we became convinced that our contribution to the training of scientific personnel for this very short field was inadequate; we did not push to the limit the training resources of the National Institutes of Health. These fellowships appear as full-time positions because this is the way we handle training at the National Institutes of Health. They are, indeed, employees; they will stay with us for no less than 2 and probably 3 years. They will be put through a rigorous training experience; they will leave and help to populate the departments of pharmacology and clinical medicine across the Nation.

Now, they don't constitute an expansion, in the ordinary sense of the word, of our own scientific capabilities. As a matter of fact, they constitute a positive drain on our resources, but one we feel we should accept as normal because of the superior environment we have in this particular area. The contribution we will make to welfare and manpower will much more than compensate for taking on what is an educational function.

ANESTHESIOLOGY

Mr. FLOOD. Do you recall last year this committee indicated a very special interest in anesthesiology, almost to the point where we felt we were prodding you? What happened?

Dr. STONE. Well, I would say we were stimulated rather than prodded. This committee's stimulation and the appropriation of at least an additional million dollars for clinical training in anesthesiology was crucial. I think funds were provided in the amount of $500,000 for research and training centers in anesthesiology. I am happy to report that grants have come in which will more than oversubscribe the research and training center part of the program.

In addition, we have on hand now 65 requests for clinical training grants in anesthesiology and they are requesting four to five times the appropriated amount.

What this means is that the need foreseen by this committee was real; it was crucial, and with the funds provided we can do something about it.

Dr. SHANNON. This is one of the real shortages in the clinical area.

There is a great shortage in this area. The primary thrust for the training of a more adequate number of clinical anestheisologists—and I am not talking now about research scientists—comes not from the anesthesiologists themselves, nor indeed from the National Institutes of Health, but primarily from the senior surgeons who feel that substantial limitation is placed upon their ability to do good surgery by the inadequate number of well-trained anesthesiologists.

Mr. FLOOD. And men go into this field.

Dr. SHANNON. Yes, sir. Both men and women. As a matter of fact, in this area there is developing increasingly a very substantial number of nurse anesthetists who, operating under suitable guidance, do an extraordinarily effective job. Many of us feel this has to be stimulated and expanded. That is the only way of ultimately satisfying the need.

Mr. FLOOD. At this point in the record we will place your special report on this subject.

(The report follows:)

SPECIAL REPORT: DEVELOPING RESEARCH AND TRAINING IN ANESTHESIOLOGY

About 25 million operations were performed in this country in 1966, most of them requiring some type of anesthesia. Every year, most of the 4 million women who have babies receive some anesthetic during labor. Few major surgical procedures are ever performed without the use of a general anesthetic. Complex operations such as open heart surgery are possible only because new anesthesiology techniques enable a patient's vital functions, breathing and blood flow, to be controlled for hours by the team of anesthesiologists.

These facts merely hint at the tremendous importance of anesthesia in modern medicine and underline the effectiveness of new anesthetic skills, procedures, and drugs which have been developed in just the past quarter of a century, developments which have been produced through comparatively limited research.

In less than 30 years new anesthetics have been developed which have reduced and in some cases virtually eliminated the period of extreme nausea, intense headache, and weakness which patients formerly suffered following most anesthesia. The President's brief visit from the press immediately after his operation last November would have been impossible only a few years ago because of the after-effects of anesthesia.

The loss of consciousness under anesthesia only partially aids surgery. Essential, too, are relaxants to insensitize and relax muscles without dangerously depressing the functions of the rest of the body. Anesthesia equipment has progressed within virtually a few decades from a bottle and a mask to today's console from which an anesthesiologist regulates the exact amounts of several anesthetics being administered to the patient. Monitoring instruments enable the anesthesiologist to observe the patient's condition closely and to vary the depth of anesthesia or assist the patient's breathing accordingly.

The skills and techniques plus the equipment of the modern anesthesiologist enable him to expand his role beyond operating rooms and intensive care units to the care of patients suffering respiratory failure from accidents, poisoning, asphyxia in the newborn, and other causes.

Despite the impressive development in clinical practice, anesthesiology research has not kept pace and still is modest in scope, due largely to the fact that up to now the field has not interested many scientists. As a result, there are critical gaps in the knowledge of anesthesiology. The mode of operation of any single anesthetic is not known. There is a real need to evaluate the use of anesthetics from the standpoint of dosage, toxicity, and patient recovery. Little is known about how other drugs, administered either before or after the anesthetic, affect the course of anesthesia and recovery. New and improved anesthetics must be developed and tested, and there is a need for further testing of some anesthetics already in use. New devices should be designed to enable the anesthesiologist to extend his services to the care of more patients. Present day operating room equipment, which presents data in a more readable form, can be improved to include calculating and determining the value of this data.

The current estimate of about 8,000 professional anesthesiologists practicing in this country is well below half the number required. By 1974 hospital admissions are expected to increase from their 1963 level—135 per 10,000 population—to 150 per 10,000 population, with 50 percent of all admissions involving surgery.

Further compounding this shortage is the fact that the role of the anesthesiologist is expanding beyond operating rooms and intensive care units to the care of patients who are suffering from respiratory failure from accidents, poisoning, asphyxia, and other causes. Moreover, advanced surgical techniques require complicated patient monitoring, often by more than one anesthesiologist for several hours of surgery, followed by hours and even days of intensive care therapy. Some hospitals cannot use their operating rooms to capacity because of the lack of anesthesiologists or paramedical personnel.

CURRENT PROGRAM

Since its establishment in 1963, the National Institute of General Medical Sciences has had the responsibility for a broad program in anesthesiology research and research training. The extent of the program, however, was quite limited ($88,000 for research in Fiscal Year 1960 under the then Division of

General Medical Sciences), mainly because the field had attracted so few researchers.

The situation changed dramatically in 1965. As part of the heart disease, cancer, and stroke program encompassed in P.L. 89–239, the Congress provided $4,550,000 in supplementary funds to the Institute for "support in areas where new knowledge and technology are urgently needed to further diagnostic and therapeutic capabilities to conquer heart disease, cancer and stroke—especially in anesthesiology, diagnostic radiology, biomedical engineering, and surgery." Following this Congressional mandate, the Institute held a meeting of the Nation's leading anesthesiologists to identify major problem areas in this field and to make recommendations for solving them.

To begin implementing these recommendations and step up its anesthesiology programs, the Institute then appointed Dr. E. M. Papper, Professor and Chairman of the Department of Anesthesiology at Columbia University and one of the Nation's foremost scientists in anesthesiology, as a "consultant in residence" for six months. Much of the improvement in the Institute's anesthesiology programs is a direct result of his efforts.

Reserach program

The key goal of the Institute's anesthesia research program is the development of better and safer methods of anesthesia and pain relief and improvement in the welfare of the surgical patient. Several facets to this program are being encouraged. Foremost of these is the improved handling of patients. The increasing complexity of modern surgery includes use of body cooling, artificial heart-lung-kidney machines, and hyperbaric chambers. The timing of injection and dosage of muscle relaxant drugs are being explored to provide not only adequate neuromuscular blocking during surgery but also fast recovery of muscular function after surgery.

Some studies are directed toward developing anesthetic agents which, while active, will also ensure adequate blood flow to the brain and other vital organs. Similar studies seek to put research findings into practice with immediate benefits to clinical medicine.

Research is being conducted which seeks useful information on how anesthetics act and on finding their direct and indirect effects on the human system. For example, current research is investigating possible harmful interactions between various disease states and the influence of anesthetic agents on renal and respiratory functions. Other research is trying to find variations in patient handling during surgery which promote more rapid recovery. The distribution of drugs and anesthetics varies among organs and tissues. The nature and extent of these variations are being studied because the receiving tissue depots determine the loading of the body and the duration and severity of long range and side effects. Finally, drug-based research is supported with the view that patient safety and well-being can be increased as improved anesthetic agents are found.

Support for research grants involving anethesiology accounted for about two percent of the research grant funds available in the Institute during Fiscal Year 1964 and 1965. In Fiscal Year 1964 the amount for anethesiology research totaled $931,000 for 11 projects, increasing to $1.2 million for 16 projects in Fiscal Year 1965. In Fiscal Year 1966 the Institute supported 27 research projects in anesthesiology with funds totaling $1.9 million. Three of the grants involve large multidisciplinary research investigations with collaboration between the anesthesiologists, the bioengineer, biochemist, biophysicist, and biomathematician.

Until Fiscal Year 1966, the research grants program in anesthesiology was concentrated in a few projects. In Fiscal Year 1965, more than half the support under this program went to a single, although excellent, project. More than $1 million of the $1.2 million provided in the program went to three projects. These projects now comprise less than 25 percent of the research program in anesthesiology.

Research training program

Research in anesthesiology cannot be conducted without well-trained scientists. During the first year (1958) of the Institute's research training activity in anesthesiology (at that time administered under the Division of General Medical Sciences), the Surgeon General approved two training programs which were funded in the amount of $30,000. This supported two postdoctoral, one predoctoral, and two summer medical student trainees.

The entire training program has grown slowly since then. In Fiscal Year 1966, 11 programs received support totaling $403,613. Limiting the growth of this much needed program has been the serious shortage of qualified anesthesiolo-

gists with sufficient time for research and research training. Not all the medical schools have departments or even divisions of anesthesiology, and nearly all the established divisions or departments face critical personnel shortages. The program, however, has managed to increase slightly the number of well-trained researchers and academicians in anesthesiology, allowing additional staffing of more teaching institutions and increasing the number of training centers. The total support of the training activity now stands at $1 million for 16 programs for about 67 trainees.

Fellowship support in anesthesiology is concentrated in the special fellowship and career development award programs and is now making steady progress in developing new research anesthesiologists. The special fellowship may be awarded to those who received their M.D. degree but who have not had prior research experience. The career development award is made to those with some research experience who want to devote the major portion of their time to research. Support in both these programs has grown because of supplementary funds provided through the heart disease, cancer, and stroke program and because of Dr. Papper's programming efforts. In Fiscal Year 1964 there were no special fellowships in anesthesiology. In 1965 one was awarded and in 1966 the number increased to 6 with support totaling $75,243. Two career development awards were granted in Fiscal Year 1964 and two more in 1965. During Fiscal Year 1966 the Institute supported 7 fellows in anesthesiology through the career development program, with support totaling $171,779.

PROPOSED PROGRAM

Research

A program for establishing a strong research effort in anesthesiology should be developed along two major lines aimed at:

1. Supporting the natural and basic biomedical sciences underlying research in anesthesiology.
2. Improving clinical care through better anesthesiological research.

A concomitant and equally important area is the training of research manpower without which this field cannot be developed.

The development of a strong research program presupposes the participation of basic medical scientists in collaborative programs with anesthesioloigsts. Such collaboration takes several forms, including these:

1. The physicist or physical chemist may collaborate with the anesthesiologist in developing instrumentation such as X-ray crystallography to determine binding sites of anesthetics on proteins and eventually to understand the molecular basis of anesthesia.

2. The pharmacologist together with the anesthesiologist could be interested in the relation of the structure of an anesthetic to its pharmacological activity, function, and toxicity with the objective of producing new anesthetic agents.

3. The physiologist and the anesthesiologist may collaborate on research in pulmonary dynamics, blood flow problems, cardiac response, etc.

4. Other basic scientists may be concerned with particular aspects of the anesthetized patient. The behavioral scientist, in particular, has a great deal to offer in the study of reaction to pain, to the surgical situation, and to stress before and after the operation.

The development of new sensing devices may permit control of depth and rate of anesthesia by computer. By using such services one anesthetist instead of the three of four now needed might monitor heart-lung operations with greater efficiency. Remote control of minor operations might be possible.

About $1,334,000 is now invested in the basic program areas involving regulation and control of the effects of anesthetics and in the patient management areas of the clinical program, the areas concerning improved handling of patients before, during, and after anesthesia.

Rapid expansion is necessary but is limited by the shortage of research manpower. The size of the program is not expected to approach much over $3.3 million in 1968, $4.3 million in 1969, $4.6 million in 1970, and $5.5 million in 1971. Large sums can be invested in hardware for developing monitoring devices. Through both grant and contract mechanisms it would be possible to invest wisely in hardware, $1 million in 1969 and larger sums in subsequent years with the possibility of a prototype model monitor within 5 years.

In broad terms, the areas requiring special research effort fall roughly into these categories:

1. *Identifying and studying the sites of anesthetic action;* determining the effects of anesthetics on consciousness and basic neural control mechanisms, especially of visceral and cardiovascular function; investigating the neurophar-

macology of inhalation agents; developing theories of narcosis; investigating the nature of pain; and studying the nature of analgesics.

2. *Studying anesthetic action at the molecular level* including investigation of drug-receptor problems; the nature of drug action when two or more drugs are combined; and drug transport at the molecular level.

3. *Developing better anesthetic application* methods, e.g., electronarcosis.

4. *Conduct of anesthesia* involving refinement of equipment to incorporate fail-safe design, to permit better control of important variables, and to achieve maintenance-free operation. This category also includes the development of better monitoring techniques, including observations of physiologic variables such as blood pressure, neuromuscular, and electrocardiogram recordings, and simplified observations of chemical variables.

5. *Improving anesthetic agents* through development and investigations of psychotropic and other new parenteral drugs, general pharmacological study of standard agents, and development and investigation of ultra-short acting narcotics.

6. *Pulmonary function and related problems*, investigation of disturbances of gas exchange in the lung, and developing methods for supporting lung function and temporary control of blood gas composition by artificial methods.

7. *Development of improved impulse blockers* and better understanding of the nature of nerve impulse blockages.

8. *Visceral functions in anesthesia*, including organ physiology and metabolic actions of anesthesia.

Support for research in these areas will continue under the Institute's research grant program and steady expansion of work in this field is expected. Indications of this expansion are apparent from the increased number of research grants in anesthesiology awarded in Fiscal Year 1966 and by the quality of the research work proposed under those grants and in pending applications. The research grants program is also beginning to feel the effect of the training programs which are beginning to produce more well-trained researchers and academicians.

In addition to support through the traditional research project grant mechanism, the Institute hopes to intensify this research by establishing research centers to carry on this work. The Fiscal Year 1967 Appropriations Bill provides $500,000 for this purpose. These centers will bring together scientists from several fields in an anesthesiology research and development program. Support for the facilities will cost about $250,000 a year after the first year. Since the centers will be the first of their kind in this field, their research will cover many of the broad categories listed above. Ideally, each center would specialize in different areas of anesthesiology research. For example, one center could combine the talents of biochemists, pharmacologists, organic chemists, and anesthesiologists to study how anesthetics work, devise and test new agents, and investigate better methods of administration. Another center could be composed of physicists, engineers, mathematicians, and anesthesiologists all working toward the goal of improved patient monitoring and automatic control of anesthesiology. From the practical view, only a few of these centers, probably not more than four or five, will be established.

Training

Two applications for new research training programs in anesthesiology have been received so far this fiscal year, and, if approved, would raise the number of such programs receiving support from this Institute to 18 and the number of research trainees to about 75.

Further growth is expected in the Institute's fellowship support in anesthesiology largely because of a new awareness in the field stimulated by the Institute's recent efforts. Because applications for special fellowships will be reviewed through April 1967, it is difficult to estimate what the increase will be in the special fellowship program. About five new career development awards are expected this fiscal year, raising the total to 12.

The Conference on Recruitment and Training for Clinical Anesthesiology which the Institute held in September 1965 recommended strongly that a program be established for training clinical anesthesiologists distinct from the present research training program. The Fiscal Year 1967 Appropriations Bill provides $1 million specifically allocated for the clinical training of anesthesiologists and represent a milestone in the Institute's history.

The clinical training program will be a model and a stimulant to the recruitment of physicians into the field. The funds will be awarded to teaching centers—schools and hospitals—for training physicians who will specialize in anesthesiology. About 10 training programs may be established with the amount appropriated, supporting about 50 trainees and providing necessary equipment and faculty.

Actual and projected amounts for the anesthesiology programs[1] of the National Institute of General Medical Sciences

	Fiscal year 1964 [2]	Fiscal year 1965 [2]	Fiscal year 1966 [2]	Fiscal year 1967 [3]	Fiscal year 1968 [3]	Fiscal year 1969 [3]	Fiscal year 1970 [3]	Fiscal year 1971 [3]	Fiscal year 1972 [3]
Research grants:									
Basic program				$1,500,000	$2,323,000	$2,323,000	$2,573,000	$2,823,000	$3,073,000
Clinical hardware [4]						1,000,000	1,000,000	1,500,000	2,000,000
Research centers				500,000	750,000	1,000,000	1,100,000	1,250,000	1,400,000
Subtotal	$931,000	$1,200,000	$1,334,000	2,000,000	3,073,000	4,323,000	4,673,000	5,573,000	6,473,000
Training grants:									
Research training	317,920	408,118	403,613	1,042,000	1,283,000	1,450,000	1,633,000	1,793,000	1,964,000
Clinical training				1,000,000	1,000,000	2,000,000	2,500,000	3,000,000	3,000,000
Subtotal	317,920	408,118	403,613	2,042,000	2,283,000	3,450,000	4,133,000	4,793,000	4,964,000
Fellowships:									
Special	none	11,670	75,243	104,000	157,000	213,000	262,000	327,000	394,000
Career development awards	38,573	46,505	171,779	228,000	266,000	337,000	412,000	507,000	691,000
Subtotal	38,573	58,175	247,022	332,000	423,000	550,000	674,000	834,000	1,085,000
Total, NIGMS	1,287,493	1,666,293	1,984,635	4,374,000	5,779,000	8,323,000	9,480,000	11,200,000	12,522,000

[1] Prepared November 1966 and amended February and March 1967.
[2] Includes only funds already awarded.
[3] Proposed.
[4] Development of patient monitoring equipment, automatic anesthesia, etc.

Mr. FLOOD. We also went to some length last year, Doctor, talking about the 5-year plan for research in behavioral sciences. I imagine there will be a proper statement in the record on the status of that program, but why not make some off-the-cuff comments about it now, if you have any?

Dr. STONE. I will put on the record that the decision is yet in the making. It is being considered by at least one committee, the Advisory Committee to the Director, and all that I will say will be of a general nature. Nowhere else do I know of a program in government dedicated to the development of the behavioral sciences as sciences. There are several programs in government dedicated to the support of the behavioral sciences in terms of what they can do for health specifically. We also will have to relate our program to the support, advancement and development of these sciences because of their real or potential use in the health field.

Our Institute, as the name implies, is one primarily concerned with the support of the sciences as undergirding and supporting the other institutes. My statement this morning emphasized this role.

Now, for a number of years, all the years I have been around, the behavioral sciences have seemed not, for a constellation of reasons unknown to me, have seemed not to enjoy the same popularity or development——

Mr. FLOOD. A constellation of reasons?

Dr. STONE. That is correct.

Mr. FLOOD. I will use that—without giving you any credit—the first chance I get.

Dr. STONE. I heard it first from Mr. Fogarty, sir. The behavioral sciences have just not received the stimulation, financial, intellectual or other, that the more regular health sciences have received.

Now, it may be that they are not thought of in many places as true biological science. I personally think of them as biological sciences. Behavioral scientists don't think of themselves as biological scientists per se, and not as medical scientists at all.

If the decision is made at higher levels for this institute to support a development program for the behavioral sciences—we will attempt to do so very much as we have done with others fields, specifically the field of biophysics, using the same techniques, and the field of genetics, using many of the same techniques, and, as I hope we will be able to do ultimately with biomedical engineering. This means, sir, that among other things we have to provide the full type of support mechanisms available to us and these are very simple mechanisms. It is rather the sophistication with which they are used which produces the results.

We will do our best to support the outstanding needs in this particular field. In the behavioral science field one of the great needs is to make computer centers available to them so that they can get baseline data, and in the behavioral science fields they seem to deal with data, just multitudinous piles and mounds of data, and they need baseline data concerning many social and behavioral characteristics of the human race.

One of the great needs that has been presented to us was for the accumulation of data which could be reproduced upon demand and, thus, each new investigator in the field did not have to go out and once again get up raw baseline data.

We do this in the natural sciences by reference tables. You can turn to reference tables and get much of the baseline data one needs. This type of thing is not available to such an extent in the behavioral field.

And in concert with many of the biological sciences, the behavioral sciences need significant exposure to mathematics and to the physiological areas as well. This does not come easily when the field is, as I believe, rather short on internal resources to support it.

Among the other things that we will provide, which are not now plentifully provided, are support for senior types of fellowships; not the senior fellowships, rather senior types of fellowships so the behavioral scientists can take sabbatical years and in a sense retread themselves in one of the other sciences so they can work at the interface between them. This is the active, growing edge between one of the basic sciences such as psychology and, if you will, mathematics or, if you will, physiology.

I hasten to add the mechanisms we will use are those legally provided. There is nothing new there. Quite frankly, it is the sophistication with which they are marshalled, which is the important thing.

These are the general things. On the other hand, there is a report which I believe is on its way to the committee which provides the position of some of our advisers. Is this correct, Dr. Shannon?

Dr. SHANNON. Yes.

PHARMACOLOGY-TOXICOLOGY CENTERS

Mr. FLOOD. Do you care to say anything else to the committee at this time concerning the pharmacology-toxicology centers which I believe were started in 1966? Would you like to make any additional statement concerning this phase of your program, Doctor?

Dr. STONE. I think I can present a picture of carefully controlled growth. I will not say "modest." That is an overworked word.

The program started in 1966 with, I believe, an appropriation earmarked at $1 million. In 1967 we requested appropriations in the amount of $3.5 milion provided for these types of specialized centers, and the same amount is requested in 1968.

Now, the problem in the development of centers is not just a scientific one. It is an administrative one, it is an educational one, and it is a financial one.

A center is not just a large grant. A center requires, if you will, interdigitation into the activities of a university center; it must be part of the educational program of a university center and for the most part it must operate clearly at the graduate level within such a center. The pharmacology and toxicology center must have availability of clinical material so that basic research can result in early clinical trials with appropriate patients. A center must have access to the chemical expertise a great university has available in a chemistry department; in the sense of modification or synthesis of needed types of drugs or modifications of a chemical into an analog that appears to have some hope of therapy without overwhelming toxicity.

In addition to this, it is perfectly obvious today that we are running into greater and greater incidence of what, in our jargon, we call adverse drug reaction. A patient on one drug is prescribed for therapeutic reasons a secondary drug and many times an untoward event takes place. This type of study is a bit new in the field. It has been done on an empirical and pragmatic basis every time a physician prescribes a drug. Such a program would be part of one of these large centers and I hasten to say that it is not a normal inclusion within much of the pharmacologic research which has gone on.

Now, a center is not an entity supported by us where any drug can be tested for any reason superficial, important, or otherwise. Basically, these centers are to do the most fundamental types of research so that drugs and chemicals can be used in research on biological systems, so that we can elaborate, if you will, the guiding therapeutic principles that would underlie the development of a drug.

We are accumulating untested drugs and chemicals at an alarming rate and I think it is unrealistic to assume that there will be biological tests for all of them. But it was the conviction of Dr. Shannon 4 years ago when he presented it to your predecessor that centers should be provided where tests upon fundamental systems, to elucidate and elaborate the principles that might be involved, a worthwhile procedure.

ULTRASOUND DIAGNOSIS

Mr. FLOOD. How about this business of ultrasound in diagnosis? I have been mixed up with ultrasound in defense for some time, but how do you use it?

Dr. STONE. We support a very few projects in ultrasound. It is a field which has at least potentially rather substantial use in diagnostic medicine. There are a series of companies that are able to fabricate useful instruments. The use of ultrasound is based on well-known physical principles and in terms of engineering rather well understood. The use of ultrasound in the clinical environment is another matter.

Now, there are several trade names—several types of ultrasonic devices on the market. The problem is to get a tracing or a visualization of the impingement of these soundwaves on, let us say, an intracranial expanding mass—it might be a massive hemorrhage; it might be perhaps a tumor.

Ultrasound is used otherwise very often to delineate, as they say, a deviated medial septum which here indicates a mass is pushing the center parts of the brain to one side, but you don't yet know what that mass is. However, those who are sophisticated in the use of the device many times can predict that it is not a hemorrhage, but it is a tumor mass. There are types of uses, as with pregnant women, where the studies of the fetus by the physician can be made without the exposures inherent in radiation.

I believe that we support a project in which ultrasound could be focused rather acutely and thus one of our investigators was able to detect tumors of the eye when they were in the small and incipient stage and had been passed over in previous diagnosis.

GENETICS

Mr. FLOOD. You have said nothing about genetics all day.

Dr. STONE. Well, I suppose this is reverse snobbery or something. I was trained basically as a geneticist and an embryologist 25 years ago; since then I have been doing this work and I have always had a rather particular interest in genetics.

When I started in the field genetics was a very interesting, clearly a university science, not accepted in the medical school. Medical school people on our campus were not terribly interested because all we did was work on fungi and fruit flies. It is interesting to look at what has happened since that time. Genetics now is one of the central disciplines, both basic and clinical, of most medical school programs. Genetics is perhaps 10 to 20 percent of the medical counseling in major departments. It relates to genetic problems of couples who intend to become married or couples who have an unfortunate familial inheritance or perhaps a child which apparently has some genetic inborn error.

Genetics, during the last 20 years has established a very active interface; perhaps a three-way interface between biochemistry on one side, physical chemistry on the other side, and the discipline of genetics on the third side. It is one of the most active areas of research at the present time, in an attempt to elucidate what is the real chemical machinery of the genetic process.

In addition to being one of the central disciplines, both basic and clinical in a medical school, it is one of the disciplines which will help us explain why a man develops as a man and a mouse develops as a mouse and an elephant develops as an elephant.

Now, my distinguished colleague, Dr. Davis, who preceded me, dealt, I think rather exceedingly well, with the DNA apparatus, at least in pictoral terms and I don't think I am capable of improving on the presentation, but the way in which the original germ cells have encoded all the information needed for the development of the future individual of which that cell is a primordium is an exquisite device. When one thinks that the total original germ cells of the human race could be placed in a 1-liter flask—over 2.5 billion people—one realizes the exquisite coding apparatus that has been developed. And when we are talking about a coding apparatus, we are talking about, basically, chemical involvement in life at the most fundamental levels.

I hope that funds will be made available so that I can support, strongly support—and my advisers are unanimous in this regard—a program of what I will call a nationally organized, but not directed, program in genetic chemistry. Which would be, in simple terms—the elucidation and elaboration of the chemistry of the genetic process.

EXAMPLE OF SUPPORT WORK FOR OTHER INSTITUTES

Mr. Chairman, I would like to digress for one moment to recount an incident which provides a rather classical example of the supporting nature to the other Institutes of research sponsored by this Institue. You will recall Dr. Shannon has emphasized the reenforcing nature of our program and I am certain you will recall the previous testimony given by Dr. Donald Whedon concerning the kidney research program of that Institute as well as the testimony immediately pre-

ceding from Dr. Dorland Davis concerning the tissue transplantation program of the Allergy Institute. One of the most exciting and important areas of research supported by our Institute is fundamental research in human genetics.

New and strong evidence for the existence of a single major histocompatibility locus in man, HU–1, has been secured by Dr. D. Bernard Amos at Duke University and Dr. F. Bach at the University of Wisconsin under National Institute of General Medical Sciences support.

This research supported by the Institute as a general study in genetics has proved to be of rather direct importance to the kidney research program supported by the National Institute of Arthritis and Metabolic Diseases and the tissue transplantation program of the National Institute of Allergy and Infectious Diseases. Since there now appear to be real possibilities for transplantation of other organs and tissues (e.g., lung, arteries, heart, liver), tremendous human benefits can be expected. These findings are clearly indicated on the basis of genetic theory and on experimental evidence obtained from animals but are of special interest because they prove that even in man the genetic system controlling histocompatibility (tissue compatability) is not too complicated to defy analysis.

In the studies at Duke University on the immunogenetics of transplantation in man, evidence has been obtained that the main transplantation antigens reside in one major chromosomal location. Several methods for evaluation are being investigated concurrently. In the studies at the University of Wisconsin the determination of histocompatability in man has been through in vitro use of mixed leukocyte cultures. An improved method for this test has been developed. The Duke and the Wisconsin studies, though different, confirm each other. It has been estimated from these data that there are 15 to 25 alleles at the HU–1 locus.

There have been many approaches to the problem of determining similarities useful to guide transplantation studies (identical twins, skin transplantation, and blood serum differences) but the serum and leukocyte typing tests of these two scientists seem simple and comprehensive. A consistency is developing in histocompatibility matching; that is, tissue compatibility evaluation. Thus, establishment of a major histocompatibility locus in man is of great importance to progress in matching donors and recipients in a transplantation program, because it provides for greater and earlier predictive reliability of which donor should be chosen.

The intellectual and scientific basis for donor typing which has been mentioned by Dr. Davis and others is a clear example of applied research made possible only by basic research developing useful information of the human genetic process.

The speed with which these findings were put to practical use came about through the informed cooperation of scientists in the field and in the National Institutes of Health, all interested in the success of a national program.

AUTOMATED LABORATORY MEDICINE

Mr. Flood. You haven't told us much about this concept of automated laboratory medicine, and the hospital computer project.

Dr. STONE. The situation facing our hospitals in terms of the reliance of the medical staff upon what is called laboratory medicine is becoming ever greater. At the present time our hospitals are approaching 1 billion such tests per year. The availability of these tests at the research level far exceeds the ability of any hospital, including our own magnificant one, to make these available on an automated basis. We can do at the research level what we cannot do under automation. It is our hope and desire that we will be able to provide in many cases the fundamental research as not to what only is needed, but also the equipment that may be needed to more clearly and purposefully automate the process.

Really, what is needed is a process where blood and urine and other primary products of the body are introduced into a machine and at the other end of the line there is an automated read-out, not only of what the constituents are, but what the normal baselines might be and perhaps the experience of that particular hospital with individuals of a similar nature.

Now, that is the goal.

Mr. FLOOD. In a town with six hospitals, could you have a central, automated service for all of them?

Dr. STONE. I believe, sir, quite frankly, that there must be centralization of much of this activity. For instance, many of these tests, even under automation, may be given, say once in 10 thousand times, or once in 50,000 times. Now, statistically a hospital can say this isn't important, but to the patient there is nothing statistical about it. To the patient who needs his kind of a test, this is a certainty.

And so I think that there must be a great deal of pooling of information and there will probably be a central laboratory, if you will, an automated laboratory, which may proceed with much of the diagnosis and at least the read-outs on the centralized laboratory tests.

Mr. FLOOD. Costs of hospitalization being what they are and what they will be, it just seems an appalling waste to have six hospitals each expending funds for these fantastic pieces of hardware at great cost, which forces up hospitalization costs. This strikes me as being a waste and a great duplication. Everybody wants to have the best. Why is that necessary? Why must they all have the best? In a town of 200,000 people and a few square miles, why?

Dr. STONE. Each one of the hospitals, if they would pool——

Mr. FLOOD. Why must all six of them have cobalt 60?

Dr. STONE. Some hospitals, sir, could not afford——

Mr. FLOOD. None of them can. That is the point I am making.

Dr. STONE. They can't afford the staff, sir, to supervise the treatment using cobalt 60 and I have had a most unfortunate experience in my own family in this situation. Expert medical care is hard to come by and not all hospitals, frankly, can provide the patient with it. I believe in the future there will be much pooling of this kind of expertise; not only in terms of laboratory hardware, but in terms of expert diagnostic qualifications which can be made available from a central source.

Mr. FLOOD. Tell us about the hospital computer program?

Dr. STONE. We are supporting a hospital computer project and have been for some years. I would say that 2 years ago I was not very sanguine about the project, but I am now very enthusiastic about this particular project, which is supported in the Massachusetts General Hospital. The problem of putting what a hospital needs, and rather particularly what the patients and the doctors and the nurses need, into a time-shared computer system has been a major problem for the group laboring in the Massachusetts General Hospital.

First, there is the sociological aversion of a physician to putting anything into a machine that he doesn't control. He will scribble on a chart, but to interpose a machine between him and some of the basic records is foreign to his training. In addition, the big development problem, once the time-sharing hardware was available, was to develop the software. That is to say, the program that would be responsive to the needs of the patient.

Well, after 4 years, the group in Boston has developed a system which is time-shared, much of the hardware is purchaseable off the shelf—and this is one of the desiderata, that as much of the equipment as could be, would be equipment which could be purchased. Thus another hospital or hospital system might be able to purchase the same equipment and perhaps modify it, but it would not be the development of brandnew hardware that was clearly unique and thus available only—even conceptually—to one unit. Now they have 65 stations that are able to use the computer and we are hoping that in the next year to 2 years they will be able to develop 260 stations that can also use this computer system.

I am not going to promise this committee that in 5 years or 3 years or 10 years this system will solve all the problems of automation in a hospital, but I think it should be a matter of concern to the committee that six commercial companies are consulting with our group as to what they would like to do in terms of automating a whole or a part of the hospital recordkeeping system. These are General Electric, Western Union, and other companies that do not now come to mind. This group has been acting, I would say, very defiinitely in the public interest by sharing their knowledge with commercial industries, as well as with groups of hospital officials who visit them. This is, I think, a healthy relationship in these matters where the maximum input has been Federal funds.

Mr. FLOOD. Thank you, Doctor, you are an excellent witness.

JUSTIFICATION MATERIAL

National Institute of General Medical Sciences

Amounts available for obligation

	1967	1968
Appropriation	$145, 113, 000	$160, 284, 000
Transfer to "Operating expenses, Public Buildings Service, General Services Administration"	−25, 000	
Comparative transfers within NIH	+968, 000	
Total	146, 056, 000	160, 284, 000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$75, 172, 000		$85, 263, 000		+$10, 091, 000
General research support grants		(6, 441, 000)		(8, 233, 000)		(+1, 792, 000)
Scientific evaluation grants		(1, 615, 000)		(1, 471, 000)		(−144, 000)
Pharmacology-toxicology research		(3, 500, 000)		(3, 500, 000)		0
Anesthesiology and diagnostic radiology centers		(500, 000)		(1, 000, 000)		(+500, 000)
Fellowships		19, 400, 000		20, 910, 000		+1, 510, 000
Training		43, 735, 000		45, 729, 000		+1, 994, 000
Direct operations:						
Collaborative research and development	2	3, 429, 000	2	3, 547, 000	0	+118, 000
Training activities	20	291, 000	30	484, 000	+10	+193, 000
Review and approval of grants	130	2, 778, 000	130	3, 023, 000	0	+245, 000
Program direction	57	1, 226, 000	59	1, 328, 000	+2	+102, 000
Total obligations	209	146, 031, 000	221	160, 284, 000	+12	+14, 253, 000
Unobligated balance, reserve		25, 000				−25, 000
Total, obligations and balance	209	146, 056, 000	221	160, 284, 000	+12	+14, 228, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	209	221	+12
Full-time equivalent of other positions	4	4	0
Average number of all employees	199	215	+16
11 Personnel compensation:			
Permanent positions	$1,903,000	$2,084,000	+$181,00
Positions other than permanent	42,000	42,000	
Other personnel compensation	32,000	32,000	
Total personnel compensation	1,977,000	2,158,000	+181,000
12 Personnel benefits	190,000	214,000	+24,000
21 Travel and transportation of persons	146,000	193,000	+47,000
22 Transportation of things	18,000	23,000	+5,000
23 Rent, communications, and utilities	112,000	152,000	+40,000
24 Printing and reproduction	19,000	24,000	+5,000
25 Other services	97,000	115,000	+18,000
Project contracts	3,393,000	3,506,000	+113,000
Payment to "National Institutes of Health management fund"	1,654,000	1,879,000	+225,000
26 Supplies and materials	57,000	58,000	+1,000
31 Equipment	61,000	60,000	−1,000
41 Grants, subsidies, and contributions	138,307,000	151,902,000	+13,595,000
Total obligations by object	146,031,000	160,284,000	+14,253,000

Summary of changes

1967 enacted appropriation	$145,113,000
Transferred to "operating expenses, public buildings service, General Services Administration"	−25,000
Unobligated balance, reserve	−25,000
Comparative transfers within NIH	+968,000
1967 total estimated obligations	146,031,000
1968 estimated obligations	160,284,000
Total change	+14,253,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
Mandatory: 1. Annualization of new positions authorized in 1967				$14,000
Program:				
1. Research grants		$75,172,000		10,091,000
2. Fellowships		19,400,000		1,510,000
3. Training grants		43,735,000		1,994,000
4. Collaborative research and development	2	3,426,000		114,000
5. Training activities	20	264,000	10	177,000
6. Review and approval of grants	130	1,540,000		59,000
7. Program direction	57	840,000	2	78,000
Subtotal, program increases			12	14,023,000
Payment to National Institutes of Health management fund for centrally furnished services:				
Training activities		17,000		
Review and approval of grants		185,000		
Program direction		23,000		225,000
Gross increases				14,262,000
DECREASES				
1 day less pay in 1968				−9,000
Total net change requested			+12	+14,253,000

EXPLANATION OF CHANGES

Research grants.—The $10,091,000 program increase includes $7,943,000 for regular projects (noncompeting continuations, $6,928,000; competing projects, $697,000; and supplementals, $318,000), $500,000 for anesthesiology and diagnostic radiology research, $1,792,000 for general research support grants and an offsetting decrease of $144,000 for scientific evaluation transferred to NIMH.

Fellowships.—The program increase of $1,510,000 includues $1,000,000 for research career development awards, $522,000 for special fellowships, and $184,000 for postdoctoral awards offset by a decrease of $196,000 in predoctoral awards.

Training grants.—The net increase of $1,994,000 reflects increases of $1,300,000 for noncompeting continuations, $2,000,000 for competing continuations, and $50,000 for scientific evaluation offset by a decrease of $1,356,000 for new grants in the graduate training program.

Collaborative research and development.—The increase of $114,000 will support minimal growth for research contracts in the program areas of macromolecular separations, pharmacology-toxicology and genetics.

Review and approval of grants.—The program increase of $59,000 will support an increase in full-time employment of professional staff required to handle the additional workload in the grants program.

Program direction.—The program increase of $78,000 and two positions will strengthen the immediate staff in the Office of the Director.

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.

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. 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 Suregon 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

	1967 estimate	Purpose
Transferred to "Operating expenses, Public Buildings Service, General Services Administration."	−$25,000	Building rental.
Comparative transfer from other NIH accounts	+968,000	Redistribution of the NIH management fund.

RESEARCH GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Regular programs	$63,116,000	$71,059,000	+$7,943,000
Special programs	12,056,000	14,204,000	+2,148,000
Total research grants	75,172,000	85,263,000	+10,091,000

INTRODUCTION

The activities of NIGMS constitute a program of fundamental research which have general relevance to, are supportive of, and essential to many categorical decisions. These activities have been centered in this Institute to provide *a central focus for many areas of science* that can best be supported and maintained within a central organizational structure. This Institute in addition has program responsibility in specially designated areas that do not logically fit into the major categorical structure of the remainder of NIH.

The categorical structure of each of the Institutes, in general, reflect their concern with a number of major disease entities such as heart disease, cancer, etc., or areas of scientific activity such as aging or child development. The programs contain a mixture of that which is fundamental to the disease under study and that which is applied and developmental. In such a structure that is an obvious need for program development oriented toward the development of a number of disciplines which underpin the activities of the several Institutes. For example, intrinsic in all categorical programs is a broad dependence on biochemistry, pharmacology, pathology, etc., and they will support research and training in each of these areas only insofar as these activities are essential for the purpose of the Institutes' specific mission—they will not in general conduct programs which will be in direct support of these disciplines as such.

The National Institute of General Medical Sciences has this responsibility and discharges it in a very specific manner. It has responsibility for the conduct of predoctoral training except so far as a minor portion is performed within a combined program project. It has the further responsibility to assay aggregate activity in both research and training and to provide for adequate balance and coverage. It must undertake specific program areas in general support and in programmed activity.

Although the National Institute of General Medical Sciences supports a broad program in most of the basic biomedical areas leading to the study of health and disease in man, it is difficult to delineate ites precise nature other than to say that the program seeks to improve clinical care and enhance basic knowledge. However, certain specific objectives can be identified with general goals and with the advancement of public health. For example, a program designed to automate clinical laboratories to provide faster, cheaper, more accurate, and more frequent analysis to aid in the diagnosis of disease would be of distinct value in the practice of medicine. The development of such a system is possible under the present state of technology, but would require relatively large sums of money to design process control and computer operation of clinical laboratories and to construct a demonstration unit. The money invested in such a program, however, would be repaid many times over in the reduction in the cost of hospital care.

Trauma is another research area offering great potential benefit to the American people. Twenty-two million bed days a year at a total cost of about $16 billion are now invested in the care of accident victims. A small reduction of even five percent in the length of hospital stay, in the cost of treatment, or in the rehabilitation of the accident patient could result in savings of hundreds of millions of dollars yearly. Again, much of the basic knowledge and technical skill are available to develop such a program. Research in this area, however, requires expensive clinical facilities and highly skilled teams of medical scientists.

Distinct improvements are also possible in the area of the clinical sciences. Every patient undergoing surgery requires anesthesiology and usually some form of diagnostic radiology. Improvements in techniques of patient monitoring.

radiology, and automated anesthesia could result in tremendous savings in the general area of patient care. In these clinical specialities, a basic-science base in biomedical engineering and control theory must be constructed before the technical innovations can be produced. As a result, goals in this area are not as sharp as those mentioned above.

A more indefinite though obtainable goal, and one of incalculable benefit to medical care, concerns application of knowledge of the structure and function of drugs to new methods of treatment in the area known as clinical pharmacology. In this field a basic structure of knowledge must be built on the metabolism of drugs with new therapeutic effects and the study of the relationship of one drug to another when they are administered concurrently. Once this basic information has been obtained, it will be possible to design drugs with greater therapeutic efficacy and lower toxicity.

Of great importance even though the knowledge they yield is not of an applied nature are programs in chemical genetics, which may provide better understanding of urban population problems, new social structures, and man's capacity for adaptation; and finally, the general support of basic science which is indispensable to the growth and development of applied research, from which eventually come practical advances in health.

The net increase of $7,943,000 for regular research grants will be used as follows: $6,928,000 for noncompeting continuations for increased costs and support of 168 additional noncompeting continuations, $697,000 for competing projects and $318,000 for supplemental awards.

The net increase of $2,148,000 for special programs includes increases of $1,792,000 for general research support grants and $500,000 for anesthesiology and diagnostic radiology centers offset by a decrease of $144,000 for scientific evaluation and planning functions transferred to the National Institute of Mental Health as part of the Public Health Service reorganization.

Program plans in 1967 and 1968

The next year will see continued support in those areas of science which offer promise for the future (genetics, molecular biology, energetics) but with a shift in support towards the physical sciences and their application to biological problems. Along with the stress to be placed on physical methods there must, of necessity, come an emphasis in practical application to bring the fruits of technology and quantitative biology to the physician and the bedside.

A program for the broad support of the basic medical sciences which may be applied to problems of human health must of necessity be very diverse. It is determined in part by the interest of the scientific community in problems of current emphasis as determined by the receipt of applications from that community. The mass of applications coming to this Institute in the form of so-called "undifferentiated" or "unstructured" applications may actually be grouped into definite programs indicating trends of science. On this basis this Institute will support programs which may eventually result in information on how cells react in disease states, bioenergetics which may be related to problems of health and basic nutrition and to the way which energy is transferred in the individual cell. Problems of human adaptability and the way in which the human organism responds to diverse environment which may some day permit man to live on the bottom of the sea or at high altitude are under exploration.

The large multidisciplinary areas of so-called unstructured research comprises about 80 percent of the budget of this Institute. Important and significant findings may be startling and unpredictable not only within the program of the National Institute of General Medical Sciences as a special case, but within any large collection of research projects where the fundamental knowledge is applied to a specific clinical problem.

Studies of the mechanisms underlying life processes through the application of the principles, concepts, and tools of biophysics, biomathematics and bioengineering are the mainstay of the biophysical sciences program. Support is provided for studies devoted to the development and application of instruments and techniques including X-ray crystallography, mass spectrometry, electrochemistry; the determination of molecular structure; and construction of special purpose equipment necessary in the investigation of the quantitative aspects of the biomedical sciences, including development of automated clinical laboratories and research on patient monitoring. Support is also provided for research projects devoted to systems analysis, feedback controls, operations research, bionics, com-

puter technology, ultrasound in diagnosis, and clinical monitoring devices and systems.

Particular stress will be placed on projects devoted to clinical applications of biomedical engineering concepts, such as clinical use of ultrasound visualization systems and their diagnostic application. Research on biomaterials concerned with the theoretical and practical application of metals and plastics in repairing or replacing tissues affected by trauma or disease will be encouraged.

Clinical research concerned with human and animal study, employing basic biochemical and biophysical principles and concepts, is the primary mission of the medical sciences program. Special emphasis will be placed upon investigation of mechanisms and treatment of burns, shock, wound-healing, tissue repair, and trauma in 1968.

PHARMACOLOGY-TOXICOLOGY PROGRAM

A program of pharmacology-toxicology centers was initiated in 1966 at a level of $1,000,000. These centers are university-based resources for both research and training and are thoroughly involved in graduate education. They are oriented to problems arising from the use of drugs and are designed to provide ready access to clinical material and to provide specialized laboratory and animal facilities. Careful consideration is given to the geographical location of these centers, as they must be able to compete for top-level scientific personnel in order to provide the scientific leadership necessary. Hence, locating them in appropriate academic, scientific, and cultural environments is given primary consideration, and has been found to be conducive to attracting the high caliber of manpower necessary.

Program plans in 1967 and 1968

Approximately 8 centers or large program projects will be supported in 1968. This includes a center now being fully developed at the University of Iowa, an active center at the University of North Carolina in Chapel Hill, and a center in clinical pharmacology at Emory University.

Under the Iowa grant, a vigorous research and training program in toxicology and biochemical pharmacology is under way. Long-range plans have been made to accommodate the center in major construction being projected for the medical school complex at Iowa City.

The project at Emory University proposes to investigate human drug metabolism and toxicology.

ANESTHESIOLOGY AND DIAGNOSTIC RADIOLOGY CENTERS

Few surgical procedures can be performed today without the use of a general anesthetic. Hundreds of thousands of patients are exposed each year to a variety of anesthetic drugs. There is a need for greater understanding of anesthetic compounds of new drugs to alleviate pain or to cause muscle relaxation and new methods for the handling of the anesthetized patient through patient monitoring devices and intensive care units. A center to explore this wide area of clinical medicine is necessary and NIGMS proposes to establish at least one such center during the coming year.

Radiology is an absolutely essential factor in assessing the damage, determining appropriate treatment, plotting the course of recovery, and evaluating the success achieved in many disease entities, including in particular coronary artery disease. The radiologist today must extend his services to more people in a given period of time which requires the development of computer techniques for storage and retrieval of X-ray film, new television techniques which will permit him to examine several patients from a central room and the development of new types of X-ray tubes and methods for the intensification of images. Such research leading to direct clinical application can best be done in a center where engineers, radiologists, basic medical scientists and physicians can be brought together in a cooperative venture to improve radiological science.

The development of a center for examination development and evaluation of new techniques in diagnostic radiology is planned in 1968 to bring the fruits of biomedical engineering to improvement of X-ray investigation and to develop new methods of visualization of tissues.

Research grants program analysis

Field	1967 estimate	1968 estimate	Increase or decrease
Biochemical sciences	$25,420,000	$27,820,000	+$2,400,000
Biological sciences	14,400,000	16,200,000	+1,800,000
Biophysical sciences	17,800,000	20,436,000	+2,636,000
Medical sciences	5,496,000	6,603,000	+1,107,000
Subtotal, regular program	63,116,000	71,059,000	+7,943,000
General research support grants	6,441,000	8,233,000	+1,792,000
Scientific evaluation and planning	1,615,000	1,471,000	−144,000
Pharmacology-toxicology research	3,500,000	3,500,000	
Anesthesiology and diagnostic radiology centers	500,000	1,000,000	+500,000
Total research grants	75,172,000	85,263,000	+10,091,000

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	1,053	$38,263,000	1,221	$45,191,000	+168	+$6,928,00
2. Competing projects	580	23,091,000	535	23,788,000	−45	+697,000
3. Supplementals	(55)	1,762,000	(76)	2,080,000	(21)	+318,000
4. Subtotal, regular program	1,633	63,116,000	1,756	71,059,000	+123	+7,943,000
5. General research support grants		6,441,000		8,233,000		+1,792,000
6. Scientific evaluation and planning grants		1,615,000		1,471,000		−144,000
7. Pharmacology-toxicology research		3,500,000		3,500,000		
8. Anesthesiology and diagnostic radiology centers		500,000		1,000,000		+500,000
9. Total research grants	1,633	75,172,000	1,756	85,263,000	+123	+10,091,000

FELLOWSHIPS

Total fellowships:

1967 estimate	$19,400,000
1968 estimate	20,910,000
Increase or decrease	+1,510,000

INTRODUCTION

The aims of the Research Fellowships Program of the National Institute of General Medical Sciences are two in number. One is to increase the supply of manpower for the research needs of the country by the support of young capable investigators reviewed on an individual basis, and, secondly, to supply Special Fellowships Awards, Postdoctoral Fellowships and Career Development Awards to those more senior individuals who have already demonstrated a marked capacity for biomedical research in order to develop new skills, greater competency in clinical or basic science areas, or to permit training in multidisciplinary approaches to the biomedical sciences. This program is administered in a manner to supplement or extend the training provided through training grants.

Program plans in 1967 and 1968

Predoctoral Fellowships are awarded to graduate students who are seeking a research degree in the biomedical sciences or in the sciences which may be closely related to better clinical care such as biomedical engineering or biomathematics. Support is now provided to predoctoral research fellows in more than 120 institutions. It is anticipated during the coming year that the number of institutions in which predoctoral fellowships are awarded will gradually increase as this Institute attempts to attain, without lowering standards, a wider geographical distribution of fellowships. At the same time the number of fellowships awarded in departments which also have training grants will be decreased. It is our belief that the support of graduate students is better obtained

through the milieu of a training grant than through the support of the individual predoctoral student for those demonstrably able and productive departments that have a firm record of successful training over the years.

Postdoctoral Fellowships provide support for one, two or three years of training to individuals who have already achieved a research degree. Such programs are structured heavily towards those areas of the biomedical sciences in which new advances are being made such as clinical pharmacology and toxicology, biomedical engineering and mathematics. The development of a program in clinical pharmacology utilizing the best skills of the basic pharmacologist, together with the talents of the clinician, can be best mounted by postdoctoral training of Ph. D.'s and M.D.'s in this area. Such postdoctoral training can be achieved by the postdoctoral fellowship and by special fellowships awarded to highly competent individuals who wish to continue or increase their training in a particular area.

Special Fellowship support will be provided to carefully selected individuals interested in obtaining advanced or highly specialized training for research. Special program emphasis will be placed in such areas as pharmacology and toxicology, biomedical engineering, selected areas of anesthesiology, diagnostic radiology and surgery.

The *Career Development Award Program* provides stable support for up to five years or more for individuals who have demonstrated a capacity for research in a productive scientific environment and who have not yet obtained recognition as established investigators. In 1968 it is planned to continue program emphasis in those areas mentioned above such as pharmacology and toxicology, and biomedical engineering. Postdoctoral, Special and Career Development Awards will also be awarded in the fields of anesthesiology, radiology and surgery in an attempt to develop these fields to their fullest research potential.

Because of the decreasing predoctoral program and the rapidly increasing postdoctoral research support program proposed, the 1968 estimates will support 150 less predoctoral fellowships than in 1967, but will permit a continuation of the shift of program from predoctoral to postdoctoral emphasis. The special fellowship and the career development award category will be expanded as will certain areas of postdoctoral fellowships (biomedical engineering), while certain other areas in this latter category (organic chemistry, biology, etc.) will be decreased, resulting in slightly fewer postdoctoral students in 1968.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	1,389	$12,159,000	1,252	$13,477,000	−137	+$1,318,000
(b) Competing	88	1,176,000	89	1,390,000	+1	+214,000
2. Supplementals	(300)	178,000	(300)	182,000	(0)	+4,000
3. New grants	589	5,887,000	599	5,861,000	+10	−26,000
4. Total fellowships	2,066	19,400,000	1,940	20,910,000	−126	+1,510,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Predoctoral	1,240	$7,936,000	1,090	$7,740,000	−150	−$196,000
2. Postdoctoral	319	2,382,000	285	2,566,000	−34	+184,000
3. Special	146	1,688,000	183	2,210,000	+37	+522,000
4. Research career:						
(a) Career	44	1,180,000	42	1,180,000	−2	.....
(b) Development	317	6,214,000	340	7,214,000	+23	+1,000,000
5. Total fellowships	2,066	19,400,000	1,940	20,910,000	−126	+1,510,000

Training Grants

Total training grants:	
1967 estimate	$43,735,000
1968 estimate	45,729,000
Increase or decrease	+1,994,000

INTRODUCTION

The Graduate Research Training Grants program of the National Institute of General Medical Sciences has several fundamental goals: (1) to increase the numbers of highly qualified personnel in the basic medical sciences and in certain general clinical areas; (2) to improve the environment in which such takes place; and (3) to expand the opportunities for research training in rapidly developing sciences such as biomedical engineering.

Training grant awards now support programs in the basic medical science departments of medical school, including biochemistry, physiology, the anatomical sciences, microbiology, pharmacology, and, in some cases, genetics, biophysics, and related fields. About 80 percent of all trainees are seeking the Ph. D. degree but support is provided for a large number of postdoctoral research trainees in certain clinical and non-clinical areas such as anesthesiology, radiology, surgery, pathology, epidemiology, and clinical pharmacology.

Because many of the biomedical researchers are not trained in medical schools, approximately one-third of NIGMS training grants supoprt basic biological and behavioral, science training programs in university graduate schools, schools of public health, schools of veterinary medicine, and, to a limited degree, schools of engineering (biomedical engineering program).

During the current fiscal year, the research training program will provide support in more than 20 different disciplinary areas, and more than 4,000 individuals as full-time predoctoral trainees and about 1,000 postdoctoral trainees will receive training. Recent data indicate that NIGMS supports about 40 percent of all predoctoral biomedical science training in the United States.

The net increase requested for 1968 will support increased costs of noncompeting continuations and 20 additional competing continuations.

Program plans in 1967 and 1968

Attempts were made last year to increase the quantity and quality of research training programs in surgery, radiology, and anesthesiology because of the marked deficit in qualified researchers, and in those competent to train others, in these areas so vital to the diagnosis and treatment of disease.

As a result, increases in both the number of students and number of programs were made. During the current year the programs will continue to expand at a modest rate. Present indications are that the trainees in anesthesiology (research) will increase from 29 in 1967 to 78 in 1968; in radiology from 6 to 45 in the same period, and in surgery from 18 to 122. New training programs in clinical anesthesiology will be launched to improve the quality of clinical care and bring the latest research innovations, after trial and evaluation, to the bedside.

The Institute feels that it is important that emphasis be placed on increasing the number of full-time students working toward a definite career goal. As a result, programs are encouraged to support only full-time students on stipends. This may reduce the apparent count of students, many of whom were previously supported on a part-time basis.

The training grants are heavily concentrated in the predoctoral training areas where the environment is an important factor in training for the beginning graduate student.

The funds available in 1968 will permit the continuation of 20 high quality training programs in areas of research emphasis such as biomedical engineering, surgery, radiology, and anesthesiology. At the same time 32 programs of lesser quality will be phased out. Because of increased costs, the 627 continuing programs will cost more than the 645 programs supported last year.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	532	$35,900,000	520	$37,200,000	−12	+$1,300,000
(b) Competing	85	5,500,000	105	7,500,000	+20	+2,000,000
2. Supplementals	(20)	585,000	(20)	585,000		
3. New programs	28	1,500,000	2	144,000	−26	−1,356,000
4. Scientific evaluation and planning	(4)	250,000	(4)	300,000	0	+50,000
5. Total training grants	645	43,735,000	627	45,729,000	−18	+1,994,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Graduate	625	42,485,000	607	44,429,000	−18	+1,944,000
2. Clinical training anesthesiology	20	1,000,000	20	1,000,000		0
3. Scientific evaluation and planning	(4)	250,000	(4)	300,000	0	+50,000
4. Total training grants	645	43,735,000	627	45,729,000	−18	+1,994,000

Training grants program analysis

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Medical sciences	138	10,196,000	141	12,101,000	+3	+1,905,000
Biochemical sciences	168	11,046,000	163	11,071,000	−5	+25,000
Biological sciences	244	14,445,000	230	14,614,000	−14	+169,000
Biophysical sciences	75	6,798,000	73	6,643,000	−2	−155,000
Clinical training anesthesiology	20	1,000,000	20	1,000,000		0
Subtotal	645	43,485,000	627	45,429,000	−18	+1,944,000
Scientific evaluation and planning	(4)	250,000	(4)	300,000	0	+50,000
Total training grants	645	43,735,000	627	45,729,000	−18	+1,994,000

Collaborative Research and Development

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	2	18,000	2	21,000		+$3,000
Other expenses		3,411,000		3,526,000		+115,000
Total	2	3,429,000	2	3,547,000		+118,000

INTRODUCTION

This activity supports by contract research programs that are developmental and applied in nature. These research projects are carefully directed by Institute staff toward the mission of this Institute. This Institute performs a large portion of its research effort through unsolicited applications necessitating a carefully constructed contract program of research and development in order to provide sharp focus to areas of particular interest. 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 1967 and 1968:

Automated laboratory medicine.—This program is an attempt to 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. The automated laboratory medicine program will be closely coordinated with the Pathology Department of the Clinical Center.

Increasing numbers of clinical laboratory procedures are considered necessary. 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. The Veterans Administration hospitals alone performed some 44 million tests in 1965.

In addition to the problem of handling the massive amount of data now obtained on each 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 tests 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 totalling $500,000 are being supported in the current year in this field. The 1968 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 1967 this program is being supported at a level of $900,000 and the 1968 estimate provides for an increase of $100,000.

Genetic chemistry.—The objectives of this program are to understand the functions of genetic material; to determine the specific sites in the molecule of 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.

This program is supported at a level of $850,000 during 1967 and 1968.

Hospital computer project.—The Hospital Computer Project is being supported in 1967 and 1968 at $700,000 by contract. This project involves the development of a computer-based hospital communication system to process patient care and clinical research data. Emphasis is on providing stable, reliable operation of the computer system in order to facilitate the collection of operating data. Additional programs will be put into service for: (1) the implementation of a hospital-wide system for reporting laboratory results, and (2) the utilization of a general information storage and retrieval system by the hospital's research community. This system is now permitting up to 64 users to use the computer simultaneously, and when completely operable, it is designed to permit 256 simultaneous

users. Documentation of the complete operation required as a part of the contract will permit other hospitals to adapt the project's techniques to their needs.

The results of the program to date have been made available to such firms as General Electric, International Business Machines, and Western Union in the interest of expediting the technology transfer to industry of this extremely important aspect of the delivery of health service.

Studies and projects conducted by the National Academy of Sciences.—In 1967 an amount of $443,000 is included in this activity and $456,000 for 1968 for the support of several projects and studies by the National Academy of Sciences. Some of the major projects include: (1) Medical Indexing of Veteran Twins. The collection of the medical histories is approaching completion on 16,000 white, male veteran twins. This will provide a resource for medical investigators who have pertinent problems in the area of genetic influences on diseases. This Institute is continuing to support this project during the current year to exploit this resource; (2) Evaluation of the NIGMS Training Grant Program; and (3) Evaluation of the Various Aspects of Postdoctoral Education in the United States. Preliminary work has begun on these two projects and it is expected that they will require two years to complete.

During the current year a study was completed on the possible connection between the anesthetic Halothane and a fatal liver disorder following anesthesia. Halothane was not found significantly associated with any single anesthesia practice. The detailed results of this study are being published in the literature.

In addition to the program expansion for contracts, there is an increase of $5,000 to support full-time employment of two positions and related costs authorized in 1967.

TRAINING ACTIVITIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	20	$197,000	30	$302,000	+10	+$105,000
Other expenses	--------	94,000	--------	182,000	--------	+88,000
Total	20	291,000	30	484,000	+10	+193,000

This intramural activity supports the training of young scientists as well as more mature investigators for both basic and applied research in pharmacology and related areas of biomedical sciences.

The requested program increase of $177,000 provides support for ten additional associates, offset by a decrease of $1,000 due to one day less pay in 1968.

At the time this program was established it was estimated that ten associates would be appointed in each of three years (1966–67–68) for a total of thirty scientists in training each year. The increase of 10 positions will permit expansion of this program to its planned level of 30 scientists in training in this field.

There are also increases of $17,000 for centrally furnished services from the "National Institutes of Health Management Fund."

Review and approval of grants

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	130	$1,322,000	130	$1,386,000	--------	+$64,000
Other expenses	--------	1,456,000	--------	1,637,000	--------	+181,000
Total	130	2,778,000	130	3,023,000	--------	+245,000

This activity supports professional and supporting staff required for the direction, review, analysis and management of research grants, training grants and fellowships. This activity also includes support for the National Advisory General Medical Sciences Council.

The program increase of $59,000 will provide for increased full-time employment to handle the increased numbers of applications reviewed and processed for an expanded grants program. Included in the net increase is $6,000 for annualization of positions new in 1967, offset by a decrease of $5,000 for one day less pay in 1968.

There are also increases of $185,000 for centrally furnished services from the "National Institutes of Health Management Fund."

PROGRAM DIRECTION

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	57	$630,000	59	$663,000	+2	+$33,000
Other expenses		596,000		665,000		+69,000
Total	57	1,226,000	59	1,328,000	+2	+102,000

This activity supports the Office of the Director, which plans, directs and coordinates the programs of the Institute, and the Program Analysis Branch which is the focal point for related data collection.

The program increase requested of $78,000 will support two new positions necessary to cope with the increasing workload related to data collection and evaluation.

Included in the net increase is $4,000 for annualization of positions new in 1967, offset by a decrease of $3,000 resulting from one day less pay in 1968.

There are also increase of $23,000 for centrally furnished services from the "National Institutes of Health Management Fund."

New positions requested, fiscal year 1968

	Grade	Annual salary
Program direction:		
Scientist	GS-15	$17,550
Clerical assistant	GS-5	5,331
Total (2)		22,881
Training activities: Commissioned officers (10)		96,000
Total new positions, all activities (12)		118,881

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. GERALD S. LaVECK, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
CALVIN B. BALDWIN, JR., EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
GERALD S. ATCHISON, BUDGET OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	2,431	3,097	3,467
11.3	Positions other than permanent	86	102	102
11.5	Other personnel compensation	33	85	85
	Total personnel compensation	2,550	3,284	3,654
12.0	Personnel benefits	272	343	387
21.0	Travel and transportation of persons	172	273	301
22.0	Transportation of things	32	47	51
23.0	Rent, communications, and utilities	105	142	156
24.0	Printing and reproduction	27	43	47
25.1	Other services	400	643	708
	Project contracts	1,233	2,799	2,957
25.3	Payment to "National Institutes of Health management fund"	2,122	2,485	2,777
26.0	Supplies and materials	183	225	249
31.0	Equipment	412	865	539
41.0	Grants, subsidies, and contributions	48,869	54,012	56,795
99.0	Total obligations	56,377	65,161	68,621

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	371	430	493
Full-time equivalent of other positions	11	13	13
Average number of all employees	311	377	419
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	37,713	40,593	42,931
(b) Fellowships	2,858	3,800	4,102
(c) Training	8,298	9,619	9,762
Total, grants	48,869	54,012	56,795
2. Direct operations:			
(a) Laboratory and clinical research	3,510	5,257	5,742
(b) Collaborative research and development	680	1,377	1,387
(c) Biometry, epidemiology and field studies	498	1,921	1,939
(d) Training	84	90	91
(e) Review and approval of grants	1,530	1,690	1,786
(f) Program direction	696	814	881
Total, direct operations	6,998	11,149	11,826
Total, program costs, funded [1]	55,867	65,161	68,621
Change in selected resources [2]	510		
10 Total obligations	56,377	65,161	68,621
Financing:			
16 Comparative transfer from other accounts	−2,763	−2,131	
25 Unobligated balance lapsing	1,409	1,892	
New obligational authority	55,023	64,922	68,621
New obligational authority:			
Current authorization:			
40 Appropriation	55,024	64,922	68,621
41 Transferred to "Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−1		
43 Appropriation (adjusted)	55,023	64,922	68,621
Relation of obligations to expenditures:			
10 Total obligations	56,377	65,161	68,621
70 Receipts and other offsets (items 11-17)	−2,763	−2,131	
71 Obligations affecting expenditures	53,614	63,030	68,621
72 Obligated balance, start of year	23,862	39,236	50,144
74 Obligated balance, end of year	−39,236	−50,144	−63,751
77 Adjustments in expired accounts	−893		
90 Expenditures	37,346	52,122	55,014

[1] Includes capital outlay as follows: 1966, $263,000; 1967, $865,000; 1968, $539,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $1,514,000 (1966 adjustments, −$10,000); 1966, $2,013,000; 1967, $2,013,000; 1968, $2,013,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. Dr. Gerald D. LaVeck, Director, National Institute of Child Health and Human Development, is before us. We have a biographical sketch of Dr. LaVeck which we will insert in the record at this point.

(The document follows:)

Name: Gerald D. LaVeck, M.D.

Position: Director, National Institute of Child Health and Human Development.

Birthplace and date: Seattle, Washington; April 19, 1927.

Education:

1948: B.S., University of Washington, Seattle.

1951: M.D., University of Washington School of Medicine.

Experience:

1966–present: Director, National Institute of Child Health and Human Development.

1966–present: Acting Scientific Director, National Institution of Child Health and Human Development.

1965–present: Clinical Associate Professor in Pediatrics, Georgetown University School of Medcine, Washington, D.C.

1963–1966: Director, Mental Retardation Program, National Institute of Child Health and Human Development.

1962–1963: Head, Crippled Children's Service, Washington State Department of Health.

1963: Clinical Associate Professor of Pediatrics, University of Washington School of Medicine.

1961–1962: Clinical Director, Rainier School, Buckley, Washington.

1960–1963: Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine.

1958–1961 :Medical Director, Rainer School, Buckley, Washington.

1958–1960: Instructor in Pediatrics, University of Washington School of Medicine.

1957–1958: Instructor in Pediatrics and Fellow in Mental Retardation, Department of Pediatrics, Neurology and Neuropathology, University of Washington School of Medicine.

1956–1957: Resident in Pediatrics, Children's Orthopedic Hospital, Seattle, Washington.

1955–1956: Assistant Resident in Pediatrics, Child Health Center and King County (Washington) Hospital.

1953–1955: Senior Assistant Surgeon, U.S. Public Health Service, Epidemic Intelligence Service, Communicable Disease Center, Atlanta, Georgia.

1952–1953: Resident in Public Health, Seattle King County Department of Public Health.

1951–1952: rotating Intern, Vancouver General Hospital, Vancouver, British Columbia, Canada.

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 (Washington) 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.

General Statement

Mr. Flood. Doctor, you might proceed with your statement.

Dr. La Veck. Mr. Chairman and members of the committee, it is a privilege for me to appear before this committee for the first time as Director of the National Institute of Child Health and Human Development. For the benefit of those of you who are new to this committee, I would like to make two points which may help in understanding our budget request.

First, we are a relatively young institute, having been established only a little over 4 years ago.

Second, unlike those institutes which are primarily concerned with one category of diseases or part of the body, this Institute 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 lifespan. The overall long-range objective of the Institute is improvement in the quality of human existence through greater scientific understanding of the developmental process.

The achievement of this goal requires that the Institute study many complex and interrelated problems. Of necessity, to most effectively utilize its resources, the Institute has had to give priority to selected problem areas. I would like to discuss some of these areas today.

INFANT MORTALITY

There is a growing concern about infant mortality rates in the United States. The yearly decrease has slowed and leveled out so that there has not been an appreciable improvement in recent years.

Mr. FLOOD. Insert in the record at this point a list of national infant mortality rates. How far down the scale are we?

Dr. LAVECK. We are No. 14.

Mr. FLOOD. Suppose you list the first 13.

Dr. LAVECK. We have the material for the record.

(The information follows:)

NATIONAL INFANT MORTALITY RATES 1965 [1]

1. Sweden	[2] 12.4
2. Netherlands	[2] 14.4
3. Norway (1964)	[2] 16.8
4. Finland	[2] 17.4
5. Australia	18.5
6. Japan	[2] 18.5
7. Denmark (1964)	[2] 18.7
8. Switzerland (1964)	19.0
9. New Zealand	19.5
10. United Kingdom	19.6
11. Federal Republic of Germany (excluding West Berlin)	[2] 23.8
12. Eastern Germany (including East Berlin)	[2] 24.5
13. Canada	24.7
14. United States	24.7

[1] Public Health Service, National Center for Health Statistics.
[2] Provisional.

Dr. LAVECK. Twelve other developed countries have lower infant mortality rates than the United States. In addition, large discrepancies exist between rates for various population groups within the United States.

The Institute considers that the infant mortality problem in this country is sufficiently serious to warrant a major effort to identify and remedy the underlying causes. The Institute has become the focal point for the coordination, stimulation and support of basic research as it relates to this national problem.

A major concern of this Institute is the stimulation and support of fundamental research which relates to various aspects of maternal and infant health and well-being. Program activities stress the identification of new knowledge which can contribute to man's better understanding of the infant mortality problem and ultimately to make it possible to correct, to the maximum extent possible, the causes of infant mortality. Program goals are three-fold and evolve around pregnancy maintenance and management, fetal survival and well-being, and disorders of infancy.

In this area of Institute concern there have been some rewarding achievements. For example, progress has been made in recent years in the management of Rh hemolytic disease or erythroblastosis fetalis. Caused by an incompatibility of blood between mother and fetus,

the condition is responsible for a large number of deaths among newborns.

During the past year, an Institute grantee in New York summarized the success of using a technique called amniocentesis to reduce fetal deaths in Rh-affected pregnancies. First developed in New Zealand, this technique has become a highly successful aid in saving babies in these pregnancies. In amniocentesis, a needle is inserted into the amniotic sac, from which some of the fluid which surrounds the fetus is withdrawn. Analysis of the fluid indicates whether the fetus is in danger from Rh hemolytic disease. The procedure has the advantage of signaling the need for pregnancy intervention and transfusions.

In about 400 pregnancies where Rh was a problem and amniocentesis was used, perinatal loss (stillbirths plus neonatal deaths) was 9 percent of the total number of Rh-affected babies. Prior to the time when amniocentesis was used in the management of Rh-sensitized pregnancies, perinatal loss due to Rh was 30 percent of the total number of Rh-affected babies.

Of still greater interest are recent developments in the attempt to prevent the occurence of Rh-sensitization. Several Institute grantees, as well as scientists in England and Germany, have found that administration of anti-Rh antibody gamma globulin within a few hours after delivery of the first baby prevents the formation of antibodies.

The first baby is rarely in danger in these pregnancies. However, passage of blood from the fetus to mother at delivery or before introduces fetal cells into the mother's blood which may start the slow development of anti-Rh antibody in the mother. Subsequent fetuses are thus affected by a reaction initiated by the first Rh-positive infant.

Although these studies on an immunizing agent are in the preliminary stages, virtually total protection has been achieved in more than 250 women in clinical trials. The use of this agent promises to eliminate Rh incompatibility as a factor in infant mortality.

BEHAVIORAL SCIENCES

The scientific exploration of the entire life process is a research task of unprecedented scope. The role of the behavioral sciences in this exploration is clearly set forth in the legislative history and the law which establishes the Institute. The behavioral sciences are not just concerned with one phase of life or with one problem. Rather, behavioral studies begin at the reproductive level and extend logically through the period of adult maturation and aging.

We are building a strong behavioral science program to make an integrated multidisciplinary approach to our basic mission—the study of man's life cycle. In examining the entire lifespan of human development, the behavioral sciences have an opportunity to enhance our understanding of what determines a particular behavior. This understanding may then lead to ways of improving behavior.

For example, the Institute is supporting studies on the effects of environmental deprivation on central nervous system development. Recently a group from the University of California at Los Angeles has described studies with rats in which environmental conditions were sufficiently profound to alter brain weight and various biochemical systems. Rats maintained for 30 days after weaning under

conditions of environmental complexity or enrichment differ significantly from their isolated littermate controls. The rats in the enriched environment had heavier brains and greater acetylcholinesterase activity than the isolated rats.

At the upper end of the age spectrum, researchers interested in psychological processes in the aged have long recognized that the elderly experience more difficulty in learning than their younger associates. A recent series of studies at Duke University's Center for the Study of Aging and Human Development has shown that this learning deficit of older people is not as great as generally believed. This Institute-supported research has demonstrated that the elderly learn nearly as well as their younger companions but because of increasing anxiety may refuse to respond.

The scientists at Duke considered learning as actually encompassing two processes: the acquisition of information, and performance involving the use of this information in response to some stimulus. Test results showed that, as result of greater anxiety, older people seem to be hampered in the latter, or performance aspect of the process.

These are only two of the many projects supported by the Institute which are designed to provide basic information about mental, emotional, social, and biological development. In addition, a major thrust of the Institute's behavioral science activities is to develop knowledge that will make it possible to evaluate and fully utilize the intellectual potential of each child. For instance, a number of studies are directed toward maximizing language acquisition, learning capacity and personality development among disadvantaged children. Studies of the potential relationship between malnutrition in early life and intellectual development in an improverished Guatemalan village are now in their second year and companion studies on marginally malnourished U.S. groups are now under development. Still other research is in progress to explore how biological and behavioral factors interrelate to shape human development.

FAMILY PLANNING

I would like to turn now to another problem area on which the Institute is focusing its attention, namely research in family planning. The problems of excessive population growth and the subsequent need for family planning research and services is receiving increasing attention throughout the country. Our Institute has the responsibility for promoting and supporting research in this important area. The Institute has three general areas of interest: reproductive biology, social and psychological aspects of family planning, and contraceptive methods.

Of current interest is the family planning practices of American families. Last year the Institute awarded a contract to a Princeton University research team to study this problem. The investigators have just published preliminary findings of the survey which indicate that an estimated 6.4 million married women have used oral contraceptives and that approximately 3.8 million are using them right now. The Institute has particular concern about the oral contraceptives which are in such wide use. We have a coordinated and expanding program to develop information which will clearly set forth the immediate and

delayed effects of this remarkably effective method. In addition, the Institute is supporting a number of research projects which may lead to new and more effective methods of contraception.

MENTAL RETARDATION RESEARCH CENTERS

I would like to mention the Mental Retardation Research Centers program. Under this program, administered jointly by the Institute and the Division of Research Facilities and Resources, four institutions received awards this year. A total of 12 institutions have now received aid for the construction or the equipping of mental retardation research facilities.

The cost of new construction and remodeling under this legislation totals $42,921,004 for the 12 centers. Of this amount, the grant awards total $25,207,675 under the 1963 congressional legislation authorizing the Public Health Service to provide matching funds for the construction of facilities for mental retardation research. It is estimated that 2 years after completion of construction of the research centers approximately 1,190 investigators would be engaged in research relating to mental retardation and related aspects of human development.

The planning and development of these research centers is a complex process requiring 3 to 5 years from initial planning to occupancy. The first two Mental Retardation Research Centers constructed under this program authority are planned for operation and occupancy in 1967 and three should open in 1968.

Mr. FLOOD. Will you tell us where they are located?

Dr. LAVECK. Centers will be located at the University of Washington, Seattle; Albert Einstein College of Medicine, New York; Children's Hospital in Cincinnati; the Walter E. Fernald State School in Waltham, Mass.; the George Peabody College for Teachers in Nashville, Tenn.; the University of Chicago; UCLA; Boston Children's Hospital Medical Center; the University of Kansas; the University of North Carolina; University of Colorado Medical Center, and the University of Wisconsin.

In planning the centers, attention was given to the need for prompt translation of research findings into service programs. The Institute plans a coordinated effort with the administration of each center to implement this objective.

During the interval between award and completion of construction, the Institute's staff initiates consultation and assistance to the awardee to assure that research and training programs are in operation or in readiness when the facility is opened.

We are looking forward to the opening of these centers for they promise to make a significant contribution in our battle against mental retardation.

INTRAMURAL RESEARCH

Construction and planning of facilities for our intramural research program have been moving along at a steady pace. The new building for the gerontology branch in Baltimore is scheduled for occupancy in the late fall of 1967. We have renovated more space at the National Naval Medical Center for a small mental retardation biomedical and behavioral research laboratory to support the children's

diagnostic and study unit. The children's diagnostic and study unit is an outpatient research facility for the mentally retarded. Also, the reproduction research facilities on the grounds of the medical school in Puerto Rico, to be shared with the National Institute of Neurological Diseases and Blindness, are due for completion in the fall of 1969.

RESEARCH TRAINING

It has been clear since the Institute was organized that the most crucial problem it faces is the critical shortage of research personnel in fields pertinant to the Institute. The ability of the Institute to develop successful research programs is dependent on how well training programs alleviate the manpower shortages that continue to exist in fields essential to the Institute's programs. In our training programs, we seek to produce researchers who will have the skills and the interest to expand our present meager 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.

The training review committees established last year for aging, reproduction and child development and mental retardation have proved to be an effective mechanism for making the best use of our training dollars. With the increases in training funds granted us by Congress in fiscal years 1966 and 1967, there has been a satisfactory level of support for approved training grants, fellowships, and development awards. We have not had to deny support of approved applications. Manpower in the nonclinical disciplines seems to be increasing at a faster rate than in the clinical disciplines. The Institute anticipates that it may need to incorporate support for appropriate residency training into its research training programs in order to ensure an adequate level of clinical emphasis on maternal and child health and development.

The Institute has had an active and productive year, with solid accomplishments of which it can be justly proud. Problem areas have been carefully identified and the Institute has developed strategies aimed at solving these problems.

For our activities in the coming fiscal year, we are submitting a request for $68,621,000. This compares with a base of $65,161,000 for 1967, and represents an increase over the 1967 comparative operational budget of $3,460,000. For grants we are requesting an additional $2,783,000; of which $2,338,000 is for research and $445,000 is for fellowships and training. For direct operations we are requesting an additional $677,000.

I shall be happy to answer any questions.

SUMMARY OF BUDGET REQUEST

Mr. FLOOD. Your adjusted appropriation for 1967 is $67,053,000. Your request for 1968 is $68,621,000. You have a reserve for 1967 of $1,892,000. I take it for granted that all of you have the same story about what gave birth to this reserve for savings, or do you know what the current story is?

Dr. LAVECK. I would like to summarize this reserve for you if I may. Of this reserve, $1,698,000 is for research grants. The reserve on

research grants was the result of a computer-based estimate of noncompeting continuation equirements made over a year ago which has proved inaccurate; $194,000 comes from direct operations. As a result of the BOB reserve, NICHD will not be able to fund approximately 46 research grants. Thirty of these are in the area of reproduction, 13 in growth and development, two in mental retardation and one in aging.

RESEARCH GRANTS

Mr. FLOOD. You have an increase of $2,338,000 for research grants. That will enable you to finance 56 projects more than this year?

Dr. LAVECK. That is correct; however, only nine will be new. The remaining 47 are noncompeting continuations.

Mr. FLOOD. What are you giving particular emphasis to?

FAMILY PLANNING

Dr. LAVECK. To be specific, we are asking for $357,000 for research in family planning. As I mentioned, this is a priority area as far as the Institute is concerned. We lack basic knowledge about the reproductive process. It is amazing to note that such basic processes as ovulation, fertilization and implantation are very poorly understood.

Mr. FLOOD. At this late date.

Dr. LAVECK. That is right. We don't have the fundamental knowledge that is essential to develop methods aimed at clarifying the problems of sterility and fertility. In fact, the mechanism of action of the intrauterine devices which are widely used is not understood at this time.

Mr. FLOOD. It gives us the impression every once in a while that you are chasing will-o'-the-wisps in some of your research. Here is something as basic and fundamental as the items you just mentioned and we are in a state of abysmal ignorance; and yet about things not so basic, we know quite a good deal. Of course, that isn't your fault, I suppose, is it?

Dr. LAVECK. We recognize this. We allocate approximately 80 percent of our funds in reproduction to fundamental problems on reproductive biology. This is where the emphasis of our program lies. Until we can uncover some of the basic mechanisms, the development of additional techniques for family planning certainly will lag.

Mr. FLOOD. How many of the 56 projects does this embrace, two?

Dr. SHANNON. Mr. Flood, could I comment? Dr. LaVeck has set forth the areas to which he expects to give program emphasis. Beginning at page 269 of the justifications is a series of estimates that present his best judgment on the distribution of funds. I don't believe he has gone to the point of allocating them as line items for such a purpose—and I would not want him to give that impression—but at this particular point in time, knowing the research grant applications that are coming in, he has indicated the areas to which he is going to give priority. The areas are research in family planning, infant mortality, growth and development, and aging. They have the major program emphasis, in addition to the program in mental retardation, for which physical facilities will become available in 1968, when the Institute begins to occupy the facilities that we have purchased or have helped to construct.

Mr. Chairman, I don't want you to feel that the allocation is so strict that he has just so many programs or so many projects for the fiscal year. These are educated estimates of what the likely distribution of these additional funds would be.

Mr. FLOOD. By the time he gets to the low man on the totem pole on these subjects, it is going to be pretty thin.

Dr. SHANNON. He will not get to the low man on the totem pole in these projects. I might say again, the mathematics is fairly rough when one estimates the number of projects by formula. At the time these calculations are made, one can only take the average cost of the projects and divide it into the total dollars assigned to the function and then you come out with a certain number which is a likely number of projects.

As you, yourself, have pointed out, if the increased cost of business is some 4 percent or 5 percent, you don't get much with a budget increase of 5 percent. If Dr. LaVeck does, indeed, at this point in time, make the grants that are proposed in the budget, it means there will be no funds of a supplemental nature to carry the increased cost of grants already in existence so that those supplemental needs that result from increased costs of doing business will have to be supplied from other sources.

Mr. FLOOD. Other sources?

Dr. SHANNON. From the community, from the institutions, from the hospital, or the medical school, or the scientists will do less work.

INCREASE IN PERSONNEL

Mr. FLOOD. Now, Doctor, you have the largest increase in personnel of any institute. You are asking for 63 additional positions. That is an increase of 15 percent. I would suggest you better have a pretty good story for all these people.

Dr. LAVECK. As I mentioned, a new facility is being constructed in Baltimore for the study of aging. It is to be located on the grounds of the Baltimore City Hospital. This will be a building containing over 90,000 net square feet of space and will house 300 NICHD employees. We are asking for 30 positions to add to the 120 positions already assigned to the Baltimore facility for research in aging. This total of 150 positions will allow us to staff this operation at 50 percent of capacity during fiscal year 1968.

Mr. FLOOD. How many floors are in the building?

Dr. LAVECK. It has four stories with a two-story mechanical wing. This will be a resource that we certainly plan to fully utilize.

In addition, we will acquire new space in the Auburn Building, which is a building located just off the grounds of the NIH reservation. This will be vacated by NINDB and NCI and we will have 18,000 square feet of space in that building as temporary space. We propose to employ 13 individuals working in the area of reproduction, 12 in growth and development to utilize the laboratory facilities that will be made available to us in early 1968, and 6 in mental retardation.

In addition, in 1968 we will acquire 23 beds in the Clinical Center. Until now we have not had bed space there. We will also have additional laboratory space of about 4,400 square feet in the Clinical Center. These are the major facilities that are now being made available to us.

Mr. FLOOD. The 63 additional people will go into these facilities?

Dr. LAVECK. That is correct. 61 new staff members will be assigned to the facilities I have mentioned.

Dr. SHANNON. Mr. Flood, I would emphasize this Institute will not get its full space and laboratory buildings in less than 3 years. We have found it absolutely essential to begin collecting the key core staff groups that eventually will operate a fairly elaborate program. Even in a situation of great scarcity of funds, recruitment of top-flight scientific personnel——

Mr. FLOOD. I thought you had dozens of them just waiting to be hired.

Dr. SHANNON. That is another story, sir. If we had a reasonable salary structure, we would have no difficulty in recruiting, but our problem is to get people who are excellent and who feel, in addition, that the opportunity to work within the National Institutes of Health is, in itself, so unique and so advantageous to their careers and for what they want to do that they are willing to sacrifice substantial salaries in order to move into our environment.

THE LEARNING PROCESS

Mr. FLOOD. Are you aware that last year we stressed at the hearings and in the report emphasis on the learning process?

Dr. LAVECK. Yes, sir.

Mr. FLOOD. We made quite a point out of that. What are your plans?

Dr. LAVECK. This is one of the areas in the behavioral sciences that we have been very interested in and concerned about and as of October 1966 we were supporting approximately 102 grants at a total cost of $3.7 million. We are interested in the behavioral aspects of learning, motivation, the effects of deprivation, educational techniques, as well as the biological aspects of learning. If you would like, Mr. Chairman, I would be happy to mention just a few of the types of projects that we are supporting. I did mention the study on learning being conducted at Duke University using elderly individuals. We also are supporting a study at New York University to investigate factors that may influence linguistic or verbal modification of perceptual responses which are believed to control the learning of much complex human behavior. A clearer understanding of these factors could lead to improved methods of teaching reading, reversing the learning of prejudice, and facilitating the discrimination of determining emotions.

Mr. FLOOD. Reversing the learning of prejudice?

Dr. LAVECK. Perhaps that is not very well stated, Mr. Chairman.

Mr. FLOOD. What does it mean?

Dr. LAVECK. They are trying to assess the effects of preconceived labels on the learning process. These findings might have implications for understanding the development of attitudes about racial, religious and national groups.

Mr. FLOOD. Don't you learn prejudice?

Dr. LAVECK. Yes, you do, but prejudices or stereotypes also may interfere with learning as well. I think the techniques that they are exploring are those that will attempt to eliminate these factors.

EFFECT OF NUTRITION ON INTELLECTUAL DEVELOPMENT

Mr. FLOOD. This may strike the curiosity of one of the Members: "A field study in Guatemala to investigate the impact of nutrition on intellectual and physiological development."

Dr. LAVECK. This is a very important area in that it is not known at this time what effects nutrition may have on intellectual development.

Mr. FLOOD. Why Guatemala? Why not Haiti?

Dr. LAVECK. It might have been Haiti. It happens that by working with the Pan American Health Organization and the Institute for Nutrition of Central America and Panama, we found the research competency there to conduct a large, long-term study to assess the importance of nutrition. The design of this study provides for the participation of families from four to six villages in Guatemala; half of the villages will serve as controls. That is families in the control villages will not receive supplemental feedings of any kind. They will receive their regular diet. The other villages will receive extra protein in addition to regular diets. Medical, psychological, and social evaluations will be conducted and children will be followed for their first 6 years of life. The physical and intellectual development of those who receive extra protein will be compared with those who do not.

I think with this type of longitudinal study we will once and for all be able to say whether nutrition is indeed important in intellectual development.

Mr. FLOOD. This is no real experiment, is it? Is there any doubt about this?

Dr. LAVECK. Oh, yes. There is no precise experimental evidence in humans proving that malnutrition leads to subnormal intelligence. A few studies suggest that severe protein malnutrition causes mental retardation and failure of normal brain growth. However, adequate control of other variables such as infections, educational opportunities, and cultural deprivation has not been achieved. Efforts will be made to control these factors in the project conducted in Guatemala so as to isolate the effects of nutrition from other variables known to be important in intellectual development.

In animals it has been well documented that nutritional deprivation can cause impairment of intellectual development.

FAMILY PLANNING

Mr. FLOOD. Are there aspects of the family planning program that we should discuss further?

Dr. LAVECK. I would like to make a few points. I think the problem of execessive population growth is one of the most critical issues of our time. As you may know, it is estimated that in 15 years the world population will increase by about 1 billion and by the year 2000 we can expect a doubling of the world's population.

Now, in the United States food production has kept pace with population increases, but the quality of life is seriously endangered. Water and air pollution, unemployment, crime, traffic congestion and urban slums are among the Nation's immediate problems aggravated by the population crisis.

Mr. FLOOD. Supply something further for the record on this subject. (The information follows:)

THE RECOMMENDATIONS OF THE NATIONAL ADVISORY CHILD HEALTH AND HUMAN COUNCIL ON RESEARCH ON FERTILITY, STERILITY, AND POPULATION DYNAMICS

One of the paradoxes of this era of progress in scientific knowledge is the relatively limited understanding which has been achieved in the area of human reproduction. While medical advances have dramatically improved the level of health care and have sharply reduced the death rate, human fertility and sterility remain shrouded in mystery. Further research is urgently needed to develop fully effective, safe, and acceptable methods of family planning. Substantial numbers of married persons are unable to have the number of children they want, or to control when they will have them. In short, our medical knowledge has not made it possible for our citizens to exercise freedom of choice in one of the most important aspects of human life.

The role of the National Institutes of Health in general, and of the National Institute of Child Health and Human Development in particular, in overcoming this problem is clear. There is a compelling need for research on the basic phenomena of reproductive biology and of human reproduction on which can be based safe, acceptable, and efficient methods of family planning. Every effort must be made to acquire new knowledge which when applied will improve the quality of births so that each newborn will be able to develop into adulthood without handicaps. We must look forward to the day when each child is wanted, when parents will be able to exercise free choice as to the number of children they wish to have, when each fertilized egg will have the greatest possible chance to develop into an infant that will be born physically and mentally normal, and when each newborn infant will have the greatest possible opportunity for surviving and developing to productive adulthood.

The major focus of our efforts should relate to questions of fertility, sterility and population dynamics in the United States, but scientific information, when obtained, should be made available to all parts of the world. It is clear that to gain information basic to the solving of these problems it may be necessary to support research outside this country.

The NIH must openly and forthrightly express its readiness to explore all the significant scientific questions relating to human reproduction, without being pressured into assuming responsibility for the development of service functions in this field. It is the responsibility of the Reproductive Biology Program of NICHD to initiate, expand, and improve research in reproduction.

The legislative mandate for NICHD to undertake such research is stated in Section 441 of the Public Health Service Act and in the report of the House Interstate and Foreign Commerce Committee. It is most urgent that NICHD take steps to stimulate and support increased research on problems of human fertility, sterility, and family planning. This effort should be appropriate to the magnitude of the problem.

Some types of research on reproduction cannot be carried out on human beings for medical, moral, or legal reasons. Such studies can be carried out on primates and these research opportunities should be exploited to the utmost. The recent efforts by NIH to create new facilities for primate research will be of great value in studies of reproductive biology. Some of the types of research required involving human beings are:

1. Basic research in the complex biological and behavioral phonomena involved in reproduction.
2. Normal human reproductive cell development, with particular emphasis on finding means to predict or produce ovulation with certainty as to timing in the menstrual cycle.
3. The processes of fertilization, implantation and early embryonic development. These can frequently be studied in humans, particularly when such studies are carried out at the time of procedures done for patient care, such as hysterectomy for disease or a curettage for a spontaneous abortion.
4. Investigations of the causes of human infertility.
5. Studies of population levels and growth rates as related to basic research infertility, sterility, and population dynamics.
6. An examination of the complex social, psychosexual, and motivational factors which help determine both the desired family size and that achieved.

7. The influence of family size on the development of personality and character of children and parents.

8. The development and testing of new techniques of family planning.

9. Field investigations of various methods of family planning with emphasis on the measurement of their efficacy, safety, acceptability, social and psychological impact in actual use by different kinds of population groups.

Family Planning Research Program

I. DEFINITION OF THE FIELD AND ESTABLISHMENT OF GOALS

Population research is defined broadly because population growth creates problems in all fields of health, as well as health-related problems which are social, economic, and political in nature. Our approach to the field is discussed under 1) reproductive biology, 2) contraceptive methodology, and 3) the psycho-social aspects of family planning. These definitions are flexible since concepts of the field will change in time as understanding of problems alter and as problems change.

A. Reproductive biology

Population research in reproductive biology is aimed at elucidating the biological processes which may have relevance to fertility regulation. Work in this field includes studies of the development of germ cells in the male and female, the processes of fertilization, oviduct transport, and implantation. It is anticipated that significant improvements in contraceptive technology will result from the systematic study of fundamental processes.

There is a dearth of new approaches to research in reproductive biology. This certainly is true in proportion to the social need. The processes of reproduction are remarkably intricate, and they require the application of all fields of biology. For instance we know little of the process of fertilization in the human. The same is true of oviduct transport and implantation. The goal of research in reproductive biology is the careful, objective, and non-directive study of these processes.

B. Contraceptive methodology

The goals of research in contraceptive technology are the development of new methods and the assurance that all methods in use are safe. The ideal contraceptive is safe, effective, inexpensive, reversible, and acceptable. It is unlikely that any single method will fulfill all these criteria in all population groups; certainly no presently available method meets these requirements. An array of methods, suitable for different applications, must be developed.

New methods should be developed from a sound understanding of reproductive physiology. Many contraceptives in current use were not developed in this way. The traditional methods are the result of the application of the principles of common sense; they do not reflect the application of great scientific sophistication. The intrauterine device developed at the time of the use of uterine pessaries, which were thought to be effective because they occluded the passage of sperm into the uterus. It is now known that such occlusion does not occur. In fact, the mechanism of action of intrauterine devices in humans is unknown.

New developments in contraceptive technology undoubtedly will continue to result from fortuitous observations. This is not unusual in science. It is more likely, however, that new methods will derive from an organized program based on an improved understanding of reproduction. The reproductive processes, which are subtle and delicately balanced, are undoubtedly sensitive to safe and effective interruption at a number of points.

The safety of contraceptives, particularly oral contraceptives, has received a great deal of attention in recent years; this is as it should be. Contraceptives are used widely by ostensibly healthy people. It is elective medication, and there is a wide choice of methods. We must make certain that all methods in use are safe.

C. Psycho-social Aspects of Family Planning

Population research goes beyond the study of reproductive biology with its end point the development of an array of effective and safe contraceptive methods. Contraceptive technology, as important as it is, is only part of the field. Traditional, indeed primitive, methods of contraception enabled most Western European countries to restrict their population growth. The same was true in the

United States during the depression years when demographers were concerned about our national future.

The psycho-social aspects of family planning include: demography, the measurement of populations and their growth rates; sociology, the reactions of various populations groups to population pressure; psychology, the response of individuals to matters related to reproduction; and economic and political science, the response of business and political institutions to population dynamics. It includes the application of the behavioral sciences to family planning programs to aid in the development of improved services and communication with people who may wish to make use of such services. The goal is the systematic application of these sciences to the population field.

II. NICHD POPULATION RESEARCH PROGRAMS

In this section the current and proposed population research programs of NICHD are described. This activity is displayed in the two tables attached to this report. Table I shows the total funds allocated for FY 1966 and the amounts estimated for 1967 and 1968. Table 2 is a detailed breakdown of the grants and contracts for FY 1966 and shows that most NICHD population research funds support reproductive biology.

The NICHD population research program does not stand alone. The field is large and the demand for knowledge and technical ability outstrips the ability of science to respond with speed adequate to the need. We share the field with other Institutes, such as NCI, NHI, and NIAMD, which have special competences in certain fields. NIGMS has special competence and interest in pharmacology and demography. We also share interest with other agencies such as the Food and Drug Administration, the Children's Bureau, the Ford Foundation, and the Population Council.

A. Grant and Contract Program

1. Reproductive Biology

Table 2 shows that 80% of the funds allocated for population research in 1966 was devoted to reproductive biology. Most of this support was in the form of grants. Contracts are used to support a limited number of projects of special interest to Institute staff and conferences on subjects in reproductive biology. This summer NICHD will support a conference on the oviduct, and next year one on the immunological approach to contraception, a field which has been comparatively neglected in recent years. Up to this time, however, it has not seemed necessary to develop an organized contract program in reproductive biology, since the field is relatively well supported through grants.

2. Contraceptive Methodology

Despite the need for improvement in contraceptive technology, NICHD does not now support work in this field. The involvement by the Institute in this field is necessary and appropriate, however, and a contraceptive development program will be organized in the future based on a detailed and rational examination of the reproductive processes for the most suitable and promising points for interference.

NICHD activities on contraceptive methodology presently are devoted to the study of the safety and the efficacy of contraceptive techniques, particularly the oral contraceptives and the intrauterine devices. Insofar as contracts are used to support research in subjects of particular social importance and interest to the Institute, the NICHD contracts in population research have been used primarily for such studies. Indeed, special funds were appropriated by Congress for this purpose.

Before reviewing the NICHD contract program in oral contraceptives, two points should be made. The first is that the importance of the problems relating to oral contraception is modified by the fact that the technology of such contraception is changing rapidly. Recent studies in Mexico and the United States show that small doses of progesterone alone, taken every day without interruption, act as an effective contraceptive without inhibiting ovulation in most subjects. This development reassures many who are concerned about current oral methods, since the new formulation contains no estrogen, the drug most implicated in adverse reactions. This changing technology does not mitigate the need for surveillance studies, rather it calls for a flexibility in their design which will allow for adjustments to changing contraceptive methods and newly recognized problems.

The second point is that intrauterine devices are growing rapidly in use, both in the United States and overseas and NICHD will, undoubtedly, play a major role in evaluating their safety and efficacy. IUD's have proved to be remarkably effective; they are unique in that only one decision for contraception need be made. Despite the fact that there are few, if any, cases reported of death from their use, they are not innocuous; women bleed and have cramps, the devices are ejected, and pregnancies occur. Beyond this, the long-term effects have not been adequately tested.

Concern for possibly deleterious effects of oral contraceptives involves four subjects discussed in some detail by the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration (August 1, 1966).

(*a*) *Thromboembolic Disease.*—Several advisory groups have recommended studies of this problem but none have been completed. A case-controlled, retrospective study is now underway at Johns Hopkins, supported by the FDA, but more studies are certainly required.

(*b*) *Cancer.*—The resolution of this problem is one of the most difficult problems facing medicine. In order to detect a doubling of the incidence of breast cancer, for instance, at least 30,000 women, half on oral contraceptives and half not, must be followed for several years. Since most known human chemical carcinogens have a latent period of at least 10 years, studies of this subject of necessity will take a long time.

(*c*) *Endocrine and Metabolic Effects.*—Case reports and laboratory studies indicate that oral steroids affect the functions of various organs, particularly the liver and pancreas. It is known that thyroxin-binding globulin rises, that BSP and transaminase levels are altered and that abnormal glucose tolerance tests are frequently found. It is not known if these alterations indicate deleterious health effects.

(*d*) *Effects on Children Born to Contraceptors.*—Estrogens and progesterones in high doses can induce congenital anomalies in some experimental animals. Furthermore, in certain animals ova which are delayed in their normal development develop abnormally after fertilization. Both of these types of observations require the careful study of children conceived during or after the use of oral contraceptives.

The NICHD contract program in oral contraceptives is aimed primarily at finding a means to survey constantly women and children exposed to possible risk. Such a surveillance system not only will provide answers to questions concerning currently used medications but also will monitor other methods as they develop. This surveillance system requires a large population of patients who can be followed for a long period of time by scientists and physicians who have an understanding of the problems under study and the capability and willingness to study the problems adequately. A search is being made for suitable populations under appropriate medical care.

3. Psycho-Social Aspects of Family Planning

This is the least well-developed area of population research, but NICHD has supported some important work. Beginning late in FY 1965 and continuing in FY 1967, we funded a survey of American family planning practices conducted by Princeton University. The purpose of the survey was to identify the number of American women currently using oral contraceptives and other methods. Similar studies will be conducted in the future by the National Center for Health Statistics.

B. Intramural Research Program

The NICHD is establishing a Reproductive Research Branch under the direction of Dr. Roy Hertz, one of NIH's most distinguished leaders in research. This Branch will encompass a broadly-based program of clinical and laboratory investigations concerning varied aspects of human and animal reproduction. A clinical unit will be established in a local hospital to study (a) fertility and sterility, (b) problems of sexual development, (c) menstrual disorders, and (d) contraceptive methods. Dr. Hertz will also develop the research facility to be constructed at the University of Puerto Rico School of Medicine for laboratory investigations into the reproductive biology and behavior of animals, with special emphasis on primates.

The ongoing research activities of Dr. William W. Tullner will become a part of the Reproduction Research Branch. Dr. Tullner has been working in the field of reproductive biology for many years. Recently, he has begun investigations on the mechanism of action of the intrauterine device.

III. SUMMARY OF RECOMMENDATIONS

Population research is a new and relatively undeveloped field. It needs to attract the attention of both established and new investigators, and it is not yet fully worked into the network of various public and private research support systems. It takes time, perhaps three to five years, before a particular area of inquiry may achieve a critical size and intellectual maturity to compete for available funds on the basis of objective scientific merit.

It is the intention of NICHD to expand its population research program in three fields: 1) fundamental research in reproductive biology, 2) the development and evaluation of effective and safe contraceptive methods, and 3) the psychological and social aspects of family planning. Contracts will continue to be used to finance projects which deal with particularly important and urgent problems, especially projects which require long-term support and close collaboration.

Population research (family planning)

[In thousands]

	1966 actual	1967 estimate	1968 estimate
Information [1]	----------	$25	$32
Training	$1,191	1,762	1,840
Research [2]	3,837	5,513	6,238
Total estimate	5,028	7,300	8,110

[1] Represents the initiation of Scientific Information Center for Reproduction.

[2]

	1966	1967	1968
Research	$3,837	$5,513	$6,238
Grants	(3,696)	(4,203)	(4,560)
Contracts and related costs	(141)	(1,010)	(1,068)
Direct research, staff and supporting costs	----------	(300)	(610)

TABLE 2.—*NICHD population grants and contracts, fiscal year 1966*

Category	Total population research		Reproductive biology		Contraceptive methods		Psychosocial aspects of family planning	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Total	212	4,986,725	182	3,993,998	24	519,557	6	473,170
Research grants	150	3,695,703	125	3,018,617	21	425,389	4	251,697
Training grants	12	894,814	10	673,341	0	0	2	221,473
Fellowships	45	255,900	44	249,652	1	6,248	0	0
Career program	2	39,888	2	39,888	0	0	0	0
Research contracts	3	100,420	1	12,500	2	87,920	0	0

THE AGING PROCESS

Mr. FLOOD. I don't think you said enough about the aging process. I gather you start to age the minute after you are born, don't you?

Dr. LAVECK. That is correct.

The adult population departs from ideal standards of health because of two types of processes. One is disease and the other is the aging process itself.

The categorical institutes for the most part are primarily concerned with diseases such as heart disease and cancer, whereas our institute

is more concerned with the aging process itself, and the relationship of aging to diseases.

Mr. FLOOD. Would this Baltimore operation deal with this to a great extent?

Dr. LAVECK. That is correct.

Mr. FLOOD. Almost entirely?

Dr. LAVECK. Yes, that is correct.

I think any significant increase in the maximum lifespan will require an increased understanding and control of the aging process. Members of the adult population certainly change in physical, intellectual, and emotional competence as they age, and we do need basic studies to point the way to an understanding of aging.

We know that the life expectancy is far greater now than it was in the past. At the present time, the life expectancy for a male is about 67 years and for a female 74 years. In contrast, the life expectancy of a man of 50 today is not very much greater than of a man who attained that age in 1900. It is evident that control of disease is insufficient and more information on the aging process, is needed to increase the maximum lifespan.

Some of our goals are to evaluate changes in the function of organs, physiological systems and biological systems with age, and much of this is being done at the Gerontology Branch in Baltimore.

We are interested in the study of cell death. Why do cells die in the aging individual? The effect of nutrition on adult health is being assessed. Also mental performance, learning ability and memory as a function of age are receiving attention.

We also are interested in retirement, particularly the health aspects of retirement. Although we are not supporting much research at the present time in this field, we have convened several groups to discuss research on retirement. These groups of consultants have identified unique opportunities for research on the health aspects of retirement.

Mr. FLOOD. Are there questions?

Thank you, Doctor.

JUSTIFICATION MATERIAL

National Institute of Child Health and Human Development

Amounts available for obligation

	1967	1968
Appropriation	$64,922,000	$68,621,000
Comparative transfers within NIH	+2,131,000	
Total	67,053,000	68,621,000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$40,593,000		$42,931,000		+$2,338,000
General research support grants		(3,807,000)		(4,395,000)		(+588,000)
Scientific evaluation		(100,000)		(100,000)		(0)
Categorical clinical research centers		(500,000)		(500,000)		(0)
Fellowships		3,800,000		4,102,000		+302,000
Training		9,619,000		9,762,000		+143,000
Direct operations:						
Laboratory and clinical research	200	5,257,000	261	5,742,000	+61	+485,000
Colaborative research and development	46	1,377,000	46	1,387,000		+10,000
Biometry, epidemiology, and field studies	51	1,921,000	51	1,939,000		+18,000
Training activities	5	90,000	5	91,000		+1,000
Review and approval of grants	83	1,690,000	84	1,786,000	+1	+96,000
Program direction	45	814,000	46	881,000	+1	+67,000
Total obligations	430	65,161,000	493	68,621,000	+63	+3,460,000
Unobligated balance, reserve		1,892,000				−1,892,000
Total obligations and balance	430	67,053,000	493	68,621,000	+63	+1,568,000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	430	493	+63
Full-time equivalent of other positions	13	13	
Average number of all employees	377	419	+42
11 Personnel compensation:			
Permanent positions	$3,097,000	$3,467,000	+$370,000
Positions other than permanent	102,000	102,000	
Other personnel compensation	85,000	85,000	
Total personnel compensation	3,284,000	3,654,000	+370,000
12 Personnel benefits	343,000	387,000	+44,000
21 Travel and transportation of persons	273,000	301,000	+28,000
22 Transportation of things	47,000	51,000	+4,000
23 Rent, communications, and utilities	142,000	156,000	+14,000
24 Printing and reproduction	43,000	47,000	+4,000
25 Other services	643,000	708,000	+65,000
Project contracts	2,799,000	2,957,000	+158,000
Payment to "National Institute of Health management fund"	2,485,000	2,777,000	+292,000
26 Supplies and materials	225,000	249,000	+24,000
31 Equipment	865,000	539,000	−326,000
41 Grants, subsidies, and contributions	54,012,000	56,795,000	+2,783,000
Total obligations by object	65,161,000	68,621,000	+3,460,000

Summary of changes

1967 enacted appropriation	$64,922,000
Unobligated balance, reserve	−1,892,000
Comparative transfers within NIH	+2,131,000
1967 total estimated obligations	65,161,000
1968 estimated obligations	68,621,000
Total change	+3,460,000

	Base		Changes to base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built-in:				
Annualization of positions new in 1967				$47,000
Total, built-in increases				47,000
B. Program:				
1. Research grants:				
(a) Regular programs		$36,186,000		1,750,000
(b) General research support grants		3,807,000		588,000
Subtotal, research grants		39,993,000		2,338,000
2. Fellowships		3,800,000		302,000
3. Training grants		9,619,000		143,000
4. Laboratory and clinical research	200	3,804,000	61	739,000
5. Collaborative research and development	46	1,315,000		7,000
6. Biometry, epidemiology, and field studies	51	1,852,000		15,000
7. Training activities	5	83,000		1,000
8. Review and approval	83	1,056,000	1	44,000
9. Program direction	45	554,000	1	50,000
10. Centrally furnished services from the National Institutes of Health management fund:				
(a) Research supporting services		793,000		56,000
(b) Clinical supporting services		389,000		46,000
(c) Administrative management		583,000		134,000
(d) Review and approval		521,000		43,000
(e) Program direction		199,000		13,000
Subtotal, management fund		2,485,000		292,000
Total, program increase			63	3,931,000
Total increases			63	3,978,000
DECREASES				
1. 1 day less pay in 1968				−18,000
2. Nonrecurring equipment costs in 1967				−500,000
Total decreases				−518,000
Net change requested			63	3,460,000

Explanation of Changes

1. Grants.—(*a*) Research: Approximately 1,143 grants will be supported in 1968 as compared to 1,087 in 1967 and 1,065 in 1966. In addition, funds are provided for general research support grants and clinical research centers.

(*b*) Fellowships:—Approximately 206 postdoctoral and special fellowships will be supported in 1968 as compared to 190 in 1967 and 138 in 1966. Also some 104 career awards and career development fellowships will be supported in 1968 and compared to 97 in 1967 and 78 in 1966.

(*c*) Training: Approximately 143 training grants will be supported in 1968 as compared to 141 in 1967 and 128 in 1966.

2. Direct Operations.—(*a*) Laboratory and clinical research: 13 positions and $157,000 will be used in the Reproduction Program for research in reproductive endocrinology, steroid metabolism, perinatal physiology, related laboratory research in human reproduction. 12 positions and $145,000 will be used in the Growth and Development Program for research into cell growth and function

at all levels and research into the biological bases of behavior, 30 positions and $363,000 will be used in the Aging Program for the second of three phases of the gradual build-up of the research staff to house the new Gerontology Building in Baltimore. 6 positions and $74,000 will be used in the Mental Retardation Program for research into the correlates of brain metabolism and psycho-social ecology and cultural anthropology.

(*b*) Collaborative research and development: $7,000 will be used for scientific information centers in aging, growth and development, and reproductive biology.

(*c*) Biometry, epidemiology, and field studies: $15,000 will be used to strenghen the Institute program to develop descriptive and analytical epidemiologic studies to determine the extent of various problems of interest to the NICHD.

(*d*) Training Activities: $1,000 will be used to strengthen the Institute Career Development Program.

(*e*) Review and approval: 1 position and $44,000 will be used to provide the increased grants management commensurate with the overall Institute growth.

(*f*) Program direction: 1 position and $50,000 will be used to provide the increased administrative staff necessary to meet the larger demands of the growing Institute.

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.

The Public Health ServiceAct, 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 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 sections 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."

Explanation of transfers

	1966 estimate	Purpose
Comparative transfer from other NIH accounts.	+$2,131,000	Redistribution of the NIH management fund.

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$36,186,000	$37,936,000	+$1,750,000
Special programs	4,407,000	4,995,000	585,000
Total, research grants	40,593,000	42,931,000	2,338,000

Introduction

This activity supports regular research grant projects in reproduction, growth and development, aging, and mental retardation. In addition, funds are provided for general research support grants, scientific evaluation grants and clinical research center grants. The regular research grants program reflects an increase of $1,750,000 in 1968 over 1967, which includes $1,229,000 to support an additional 47 noncompeting continuations and to support an additional 9 competing projects.

The budget for 1967 and 1968 reflects the application of the newly authorized cost sharing arrangements to competing research grant projects (new and renewal). This cost sharing plan considers the full indirect cost of the research project in arriving at the Federal and nonfederal share. For continuation of previously approved projects the earlier limitation of 20 percent or less for indirect costs is applied with an assurance of some sponsor cost participation.

In addition, an increase of $588,000 for General Research Support Grants represents the Institute's proportionate share of the proposed National Institutes of Health increase in this area.

Program Plans for 1967 and 1968

Research in Family Planning.—$357,000.

The Institute's interest in this field falls into three research areas: reproductive biology, the psychological and social aspects of family planning and contraceptive methods.

Most of the grants in this field now support reproductive biology research, which is aimed at elucidating the biological processes of reproduction which may have relevance to fertility regulation. Research grants are used to support projects designed to study the development of germ cells in the male and female, the endocrinological aspects of reproduction, the processes of fertilization, oviduct transport and implantation in the uterus. The Institute shall continue to suport such investigations, in both humans and experimental animals, with the expectation that these studies will yield worthwhile information leading to the development of better and safer family planning techniques.

The recent introduction of new methods of fertility control has created rapidly changing patterns of American family planning practices. The Institute is interested in developing and supporting research which will lead to the development of contraceptive methods acceptable to a variety of population groups. The ideal contraceptive is effective, simple, safe, inexpensive, and acceptable; it is unlikely that any single method will fit all these criteria. Therefore, it is our goal to support a variety of research projects which will lead to the development of a number of effective methods.

The Institute is concerned with the immediate and long-term effects of fertility regulation. In particular, recent clinical reports and a wealth of animal research findings led to careful examination of several problems possibly related to the use of oral contraceptives. These include thromboembolic disease, endocrinological and metabolic defects, cancer, and the effects on children born to women using such contraceptives. Scientists have no reason to believe that these problems are interrelated and the research methods applied to finding solutions to them certainly will vary. Accordingly, some of the questions raised on oral contraceptives will be answered by large long-term studies and others by smaller projects designed to answer more restricted questions.

The importance of the problems relating to oral contraceptives is modified by the fact that the technology of such contraception is changing rapidly. This changing technology does not substantially mitigate the need for surveillance studies; rather, it calls for a flexibility in their design which will allow for adjustments to changing contraceptive methods and newly recognized problems.

The Institute is vitally concerned with learning more about intrauterine contraceptive devices which are growing rapidly in use, both in the United States and overseas. These devices have proven to be remarkably effective; they are unique in that only one decision for contraception need be made. Despite the fact that there are few, if any, cases reported of death from their use, they are not innocuous: women bleed and have cramps, the devices are ejected, and unwanted pregnancies occur. Beyond this, the long-term effects have not been adequately tested. The Institute will play an increasingly important role in evaluating their safety and effectiveness.

Research in Infant Mortality.—$373,000.

The death of an infant before his first birthday is a source of increasing concern in the United States. During this first year of life, the risk of dying is greater than during any other year until after age 65. In 1964, 99,783 infants died before reaching their first birthday; 72,026 of these deaths took place during the first four weeks of life, with 41,840 infants dying within the first 24 hours. While infants with birth weights of 2,500 grams or less constitute about eight percent of total live births each year, an estimated 50 to 60 percent of all neonatal deaths are of infants within this particular weight group.

Striking similarities exist between late fetal and early neonatal deaths, indicating that many of the causative factors for these perinatal deaths are part of the continuum of fetal life and are, for the most part, pregnancy related. In addition to deaths of live infants, registered fetal deaths in 1964 totaled 94,467 with 65,931 being of 20 weeks or more gestation. In considering the magnitude of the perinatal mortality problem, it must be remembered that in addition to the reported 28,536 early fetal deaths, there is a large unknown component consisting of early spontaneous as well as criminal abortions and unregistered stillbirths.

Since the majority of neonatal deaths are pregnancy related, this Institute will emphasize the identification of these pathophysiologic factors which determine a high-risk pregnancy or subject the fetus to jeopardy. Documentation of normal physiological, biochemical, or immunological processes as well as those deviations from normal development which fall outside the margins of safety for either the maternal or fetal organism are planned. Once identified, refined biomedical techniques can be applied to isolate aberrant mechanisms which contribute to fetal wastage and prematurity.

Until recently, babies weighing 5½ pounds or less at birth were considered, by definition, to be premature infants. It is now realized that these babies differ in degree of maturity achieved. Some are of shortened gestation, while others suffer from intrauterine growth retardation. These latter are the "small-for-dates" babies, while the former are prematurely born infants.

The Institute plans a multifaceted approach to the problems of these babies. The interaction of the maternal-placental-fetal complex as related to fetal growth and development will be explored. Particular attention is to be directed to the identification of reliable indices of the process of fetal maturation so that the prematurely born infant might be distinguished from the equally small full-term baby. Such knowledge is essential since physiological handicaps and subsequent health problems of these two groups of babies may be quite different and could influence their chances for survival.

About two-thirds of all low birth weight infants are prematurely born or of shortened gestation. Factors responsible for early terminations of a pregnancy are still largely unknown; it is recognized, however, that a better understanding of the entire process of childbirth is crucial to preventing premature labor as well as to initiating labor in pregnancies that are overdue.

While many theories have been proposed to explain the phenomenon of labor, it is still not clearly understood why it begins. It appears likely, however, 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 contractions characteristic of labor. Currently, the Institute is supporting a number of research grants concerned with unraveling the unknowns of this process. Researchers are studying the physiology of uterine muscle, the effects of uterine contractions on the human fetus and the particular contributions and interrelationships of the hypothalmus, the central nervous system, the placenta, the fetus, and specific hormones in the initiation of labor.

Another important area of investigation concerning infant mortality is the one seeking clues to the causes of sudden death in infants. Each year approximately 10,000 to 20,000 infants in the United States die suddenly for no apparent reason. A leading cause of death in children under one year of age, this mysterious killer, also called "crib death," strikes apparently healthy, well-nourished infants, often with no previous record of illness. Doctors don't understand it, and until now they had little but their own experience to draw upon for the answers.

The Institute has recently published the first book-length treatment of this subject, based on an interdisciplinary conference where the leading investigators and authorities on "crib deaths" pooled their knowledge and ideas for the first time. *Sudden Death in Infants* is the first definitive work in this area and promises to be the springboard for expanding research and cooperation among scientists.

An Institute-supported epidemiologic study of all sudden, unexplained deaths among infants in an entire county on the West Coast, revealed that of 155 sudden, unexpected infant deaths examined to date, 115 have remained unexplained. All of these 115 deaths occurred during the sleep period. This study has shown that the peak incidence of sudden infant deaths is in the two-to-four months age group. The mysterious syndrome spares very young infants and is rare after six months of age.

Investigations emphasizing other approaches to this problem are also being supported. These include identifying the mechanisms of sudden death, investigating the etiology of an allergic response, and determining the role of respiratory viruses in the occurrence of the syndrome. We will continue to support such research with the goal of solving the mystery of sudden unexpected death.

To date, the biological aspects of the perinatal and infant mortality problem have been emphasized; more needs to be done with the behavioral components of pregnancy maintenance and management, fetal survival, and infant well being. Research plans for 1967 and 1968 include increased emphasis on behavioral science studies in infant mortality as well as identification of interrelationships between biological and behavioral factors in this area.

Research in Growth and Developments.—$526,000.

The study of growth and development involves a multidisciplinary approach encompassing biological and behavioral sciences collaborating to understand the normal processes within individuals as they develop from birth to maturity. The impact of childhood diseases and of genetic, nutritional, or environmental (physical and emotional) abnormalities on growth and development is also emphasized. Among the many disciplines involved are those concerned with physiology in the broadest sense, intellect, learning, behavior and social influences. Research on the processes involved as the individual changes from a completely dependent infant to a mature, self-directing and productive member of society, has as its ultimate goal the knowledge needed for the achievement of optimal development which will result in improvement of quality of human existence during the growth period as well as in the subsequent years of maturity.

A better understanding will be sought of the human organism in terms of the physiological development of the species, the individual, and the components of the individual. Research efforts will deal with the biological processes and mechanisms which contribute to the uniqueness of the individual in order to learn more about the complex interrelationships between the fluctuating physical environment and the physiological function and growth of developing individuals who differ in race, residence, socioeconomic status, and other factors. A dynamic program will be established to delineate the research problems relating to the nature, establishment and development of physiological rhythms in the human organism. Additionally, the Growth and Development Program plans to develop research projects in other promising areas in order to:

(1) Further our understanding of nutrient interactions and patterns of nutrient intake which result in optimal body development and composition. Relationships between nutritional intake, growth patterns, and intellectual development will be established through studies involving alterations in nutrient intake. To facilitate these goals, the preparation and publication of a "Guide to Nutrition Terminology" suitable for classifying, storing, and retrieving nutrition information with adaptation to National Library of Medicine and other library needs will be completed by 1970.

(2) Gain a better understanding of the relationships between physiological and behavioral processes through interdisciplinary research utilizing behavioral biology. Efforts will be made through this interface between biology and behavior to identify and assess the basic biological mechanisms contributing to the development of intellectual potential and emotional control as they are affected by hereditary and environmental influences. A primary goal will be development of methodologies for assessing deficits in brain function or central nervous system damage in children who are raised during their critical periods of development in impoverished environments.

(3) Broaden our descriptive knowledge and refine our theoretical understanding of psychological development and learning, including the intellectual, social, and emotional aspects. Research efforts will span the entire length of childhood from early infancy through late adolescence and across many population groupings defined by such characteristics as sex and sociocultural status. An early goal will be a critical review of information pertaining to moral development, conduct of a conference on this subject, and possible publication of a reference

volume, in collaboration with other interested groups at the National Institutes of Health. By 1973 we will have developed methodologies, broadened descriptive knowledge, and refined our understanding of underlying mechanisms with regard to the following: the influence of parent-child interaction on child development and on parental attitudes; the role of early stimulation and deprivation in learning and cognitive development; conditions which promote creative, constructive, and adaptive aspects of personality development; interrelationships between cognitive elements and other aspects of personality development; and the development of impulse control. Major attention will also be given to developing theoretical and methodological approaches to the study of learning in children as a complex, interdisciplinary developmental process.

Research in Adult Development and Aging.—$187,000.

Research in this area is directed towards the enhancement of physical and mental health during the entire period of adult life. There are now approximately 19 million Americans over the age of 65 years. They constitute about 10 percent of the population. Thus a large segment of the population is living in a phase of life that presents serious problems with regard to health and psychological and social adjustment. Great emphasis is thus placed on the development of knowledge about medical, psychological, and social problems of the elderly. However, emphasis is also placed on the development of information about the problems of the young and middle-aged adult because of the intrinsic importance of studies that deal with that portion of the lifespan and because the physical and mental health of the elderly person is based on his health as a young and middle-aged person.

Throughout the adult years, progressive decreases occur in the efficacy of many functions from the cellular level to the level of the whole animal. These changes have a great effect on health in the positive sense of vigorous functional ability as distinguished from the simple absence of diseases and on the excellence with which a large number of physical and mental activities can be performed. They also have a heavy impact on the ability of the individual to withstand disease. This is shown by the dramatic increase in mortality rates from a very wide variety of causes with increasing age. For an understanding of the impact of disease on the elderly there must be studies not only of disease processes but also of the functional abilities of the elderly persons in whom those disease processes occur.

The early life of the individual has great effect on his later life in ways that are just beginning to be appreciated. For example, undernutrition of the young rat may double his lifespan. In the coming year the effect of such early environmental factors, the processes through which they operate, and the ways in which they can be favorably modified will be studied.

It is known that there are striking changes in the overall functional capacity of the body with increasing age. The decline in the ability to exercise vigorously is a good example of this. In addition there are less obvious changes that occur in the functional capacity of the individual organs with age. The rates at which these changes occur vary greatly from organ system to organ system and from individual to individual. There are also marked changes in the ability of the body to carry out biochemical operations with increasing age. One example of this is the change in the metabolism of fat that is reflected in the increase in the concentration of fatty materials such as cholesterol in the blood with increasing age. Another is the impairment of the body's ability to utilize sugar and other carbohydrates with increasing age. Such changes in bodily function will be studied in individuals of different ages to determine the rates at which the changes occur, the mechanisms involved, and the factors that influence the changes. Studies are of great importance from the standpoint of determining what the range of normal function is at each age, what is normal and harmless, what is disease and should be treated, what the functional weaknesses are that occur with increasing age, and what can be done to compensate for them. Such studies will have important implications with regard to the effect of various factors such as diet and exercise on health and well-being.

It is becoming increasing clear that individuals have different hereditary endowments, and that these are reflected in their physical characteristics. These characteristics are in turn modified by dietary and other practices of the individual, and by the environmental factors, toxic and otherwise, that act upon the individual. The progression of changes in physical characteristics may lead to disease processes. The developing changes can in some instances be recognized

years before they lead to overt illness. Careful long-term studies of human populations should lead to a recognition of the significance of various types of bodily characteristics and changes. This in turn will make it possible to recognize the characteristics of a person that place him in a high-risk category with respect to certain diseases. This information will be of great value in undertaking certain types of preventive care.

A great deal of research remains to be done on the biological changes that are responsible for the aging processes we recognize. Fundamentally very little is known in this area. It is clear that there is death of cells with increasing age and thus a progressive decrease in the number of cells in the various tissues and organs with increasing age. There is little change demonstrable in the structure of the remaining cells even with procedures as powerful as electron microscopy although the accumulation of insoluble materials in certain cells has been demonstrated. There are various suggestions of diminution and abnormality of function in the surviving cells of the elderly animal, but information in this area is fragmentary. Studies on the changes in cellular structure and function that occur with increasing age are underway and will continue in an effort to solve the great mystery of aging and to make possible a more rational medical response to its manifestations.

As individuals pass through life there are, in addition to biological changes, profound psychological changes. These include alterations in sensory ability, learning ability, intellectual creativity, and many other functions. Each decade of life is different and has its own potentialities and responsibilities. Careful studies of the psychological determinants of life are necessary in order that each individual may lead the most satisfying and useful life that is possible for him.

In addition what society expects of a person changes with that person's age. In particular we are moving into an era in which a large fraction of the lifespan may be spent in retirement. Thorough psychological and social studies are necessary to provide the information that will make it possible for society to make this a period of self-fulfillment rather than one of frustration. A program of such studies is now under development and will be expanded in the coming year.

Research in Mental Retardation.—$307,000.

Estimates place the number of retarded individuals in our nation today at approximately 5½ million. About 90 percent of these retardates are only mildly disabled, and in many instances can achieve partial or total economic support. They are heavily concentrated among families with poor education and low incomes. For many of the retarded population it is not yet possible to determine a specific diagnosis. The majority of retardates have no demonstrable structural brain abnormality, at least insofar as we can tell by our present instruments of measurement. Some of the problems are psychosocial in character and are often aggravated by cultural and environmental deprivation. Since psychosocially abetted retardation contributes to the self-perpetuating nature of the disadvantaged groups in our society, it is extremely important that ways be found to combat it.

We need to know much more about basic processes of motivation, perception, learning, and cognitive processes in the mentally retarded of all ages. We need a better appreciation of what could be accomplished through early stimulation and careful training of children who shows signs of being retarded.

In 1967 and 1968, the Institute's extramural program will continue research in the behavioral aspects of mental retardation. One large research project is investigating the development of language and cognition in culturally and environmentally deprived children. Considerable progress is being made in this area by teaching preschool children to think with language symbols. Researchers are using two main methods to improve the intellectually retarded child's language skills: a phonetic alphabet system with 64 letters, each representing a single speech sound, called an Initial Teaching Alphabet; and a language development kit, a program to 200 prepared language lessons including specific language plans for each day with stimulation being supplied by the use of tape recorders, puppets, and other interesting materials.

Because of the teacher's attitudes and abilities are so important in reaching deprived children, another research team is also investigating the effectiveness of teachers and educational methods on retarded children. Researchers are studying parent-child interactions in preschool training.

From preliminary results already obtained, the researchers are confident that parent-child teaching and training, such as that demonstrated in their program, may be one answer to breaking the self-perpetuating cycle of cultural deprivation.

These studies provide leads indicating that mild retardation and subnormal intellectual functioning due to cultural and environmental deprivations does

not have to be self-perpetuating. Program plans for 1968 include expanded research on such aspects as preschool enrichment and remedial instruction; education and parent-child interaction; the development of instruments and devices for evaluating learning capacities and behavior. Additional research is planned to identify means of improving public and professional attitudes through assessment of public attitudes and their impact on the retarded person's self-image and adjustment, access to social and vocational opportunities, family strategies, and mechanisms developed by retardates to cope with problems and stress situations.

In attempting to understand the biological causes of mental retardation, the Institute is supporting a comprehensive grant program in molecular biology, especially in genetics. Chromosomes are the structures in the nucleus of the cell which carry the genes. Gross abnormalities of chromosomes have been shown to be related to spontaneous abortions and birth defects, including mental retardation.

With regard to Down's syndrome (mongolism), for example, it was discovered that mongoloids have 47 chromosomes instead of 46, the normal number. The discovery raises further questions concerning the incidence and causes of this condition. Expanded research is underway to follow up this lead.

Beginning in 1963–64, researchers have surveyed 7,000 newborns in Denver, Colorado. They found that babies with abnormal numbers of sex chromosomes tended to appear in seasonal clusters, during a five-month spring and summer period. These findings were substantiated in a more recent survey. There was also a rise in the incidence of Down's syndrome during this same five-month period. There findings suggest that sex chromosomes and the autosomal chromosome involved in Down's syndrome may be equally susceptible to production of abnormalities due to some external factors. Increased attention during 1967 and 1968 will be directed toward the identification of the particular environmental factors involved.

Since the cause of chromosomal abnormalities is generally unknown, a number of possible pathways are being explored. The Colorado researchers are currently investigating the possibility that a latent virus infection in the mother around the time of conception might be one factor involved.

Chicago reseachers are studying the relation of German measles, regular measles and infectious hepatitis to chromosomal abnormalities. This group is continuing its studies of chromosome aberrations and extending them to investigations of stillbirths and spontaneous aborations.

Other research efforts are involved with studying the biochemistry of cell cultures. Since genes work through enzymes, these substances in particular are under study. Attempts are being made to correlate any biochemical and enzymatic deviation with chromosomal abnormalities.

"Genes mapping" is another area of on-going research. As yet, no specific genes have been definitely located on any of the autosomes. Mapping of gene locations on human chromosomes is of prime concern to cytogeneticists since genes carry the heredity traits. Subjects with abnormal chromosomes, and their relatives, are currently being studied clinically in hopes that specific traits can be assigned to particular chromosomes.

Radiation also seems to have a direct influence on chromosome patterns. One investigator has been able to quantify the dose of radiation necessary to cause specific chromosome breaks in tissue cultures. He is following up this work in both cell cultures and laboratory animals.

Research grants program analysis

	1967 estimate	1968 estimate	Increase or decrease
1. Reproduction	$15,945,000	$16,675,000	+$730,000
2. Growth and development	11,701,000	12,210,000	+526,000
3. Aging	3,784,000	3,971,000	+187,000
4. Mental retardation	4,756,000	5,080,000	+307,000
5. Subtotal, regular program	36,186,000	37,936,000	+1 750,000
6. General research support	3,807,000	4,395,000	+588,000
7. Scientific evaluation	100,000	100,000	0
8. Categorical clinical research centers	500,000	500,000	0
9. Total, research grants	40,593,000	42,931,000	+2,338,000

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting projects	771	$23,475,000	818	$24,704,000	+47	+$1,229,000
2. Competing projects	316	12,711,000	325	13,232,000	+9	+521,000
3. Subtotal, regular program	1,087	36,186,000	1,143	37,936,000	+56	+1,750,000
4. General research support		3,807,000		4,395,000		+588,000
5. Scientific evaluation		100,000		100,000		0
6. Categorical clinical research centers		500,000		500,000		0
7. Total, research grants	1,087	40,593,000	1,143	42,931,000	+56	+2,338,000

Fellowships

Total Fellowships:

1967 estimates	$3,800,000
1968 estimates	4,102,000
Increase or decrease	+302,000

Introduction

The fellowships program for the National Institute of Child Health and Human Development reflects a net increase of $302,000 in 1968 over 1967, including an increase of $361,000 to support an additional 29 con-competing continuations, and a decrease of $59,000 from the 1967 level for competing projects.

The net increase provides $50,000 to support an additional 7 postdoctoral fellowships, $98,000 for 9 special fellowships, and $154,000 for 7 research career development awards.

Program plans for 1967 and 1968

The interest in research covering the entire human lifespan necessitates that many scientists working on child health and human development studies have cross-disciplinary training. The fellowship awards, by providing support for additional training to experienced investigators, is one of the most effective training mechanisms.

The type of fellowship awards funded by the National Institute of Child Health and Human Development in the past will again be given strong priority in 1967 and 1968 because of the ever-increasing demands of research in these fields. Of prime importance is the training of obstetricians, pediatricians, and gynecologists. 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 specialties 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 that any be diverted from clinical care to research.

In addition to these types of training, a number of new interdisciplinary fields are developing rapidly and need fellowship support. These include many emerging areas within behavioral biology, such as psycholinguistics and behavioral genetics, both of which are strongly developmental in their approach and particularly are relevant to the Institute's research in mental retardation.

Strides have already been made in the use of psycholinguistics with mentally retarded children but the field has hardly been explored yet. This field may also have great relevance to the Growth and Development Program's attempts to evaluate and stimulate the learning process in normal children. Behavioral genetics is especially relevant to the reproduction program both in contraceptive research and in the efforts to reduce congenital defects leading to infant deaths. Genetic studies also play a major role in the search for means of preventing mental retardation caused by chromosomal abnormalities.

The Institute will also sponsor training in developmental pharmacology—a fields of vital importance to all the Institute's major program. From thalidomide

to tranquilizers. the use of drugs and anesthetics has proven to be a powerful instrument for improvement or destruction. The field is really just in the formative stage; the possibilities are many. With sufficient numbers of trained researchers, developmental pharmacology could become one of the most effective tools in the National Institute of Child Health and Human Development's attack on human health problems.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	127	$2,092,000	156	$2,453,000	+29	+$361,000
(b) Competing	31	395,000	30	387,000	−1	−8,000
2. Supplementals	(7)	15,000	(7)	15,000	(0)	0
3. New	129	1,298,000	124	1,247,000	−5	−51,000
4. Total, fellowships	287	3,800,000	310	4,102,000	+23	+302,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Postdoctoral	127	$896,000	134	$946,000	+7	+$50,000
2. Special	63	681,000	72	779,000	+9	+98,000
3. Research career:						
a. Career	8	240,000	8	240,000	0	0
b. Development awards	89	1,983,000	96	2,137,000	+7	+154,000
4. Total fellowships	287	3,800,000	310	4,102,000	+23	+302,000

Program analysis

Program area	1967 estimate	1968 estimate	Increase or decrease
Reproduction	$1,767,000	$1,780,000	+$13,000
Growth and development	1,363,000	1,393,000	+30,000
Aging	250,000	280,000	+30,000
Mental retardation	420,000	649,000	+229,000
Total fellowships	3,800,000	4,102,000	+302,000

Training Grants

Total training grants:

1967 estimate	$9,619,000
1968 estimate	9,762,000
Increase or decrease	+143,000

Introduction

This activity provides for grants to institutions for support of graduate students in the fields of reproduction, growth and development aging, and mental retardation.

The request for a new increase of $143,000 includes an increase of $1,195,000 to support an additional 16 non-competing continuations offset by a reduction of $1,052,000 in the level of competing projects.

Program Plans for 1967 and 1968

A major purpose of the Institute is to support research into the health status, needs and problems of human beings of all ages from infancy to old age. During

1967, we made some progress in supporting training of professional personnel for research in critical areas of concern—reproduction and population studies, perinatal and infant mortality, growth and development, mental retardation, and aging. However, increased emphasis on all of these areas requires that training be accelerated if we are to meet intramural staffing needs as well as those of academic institutions and other research-oriented facilities. Critical shortages of trained investigtors in such disciplines as obstetrics, gynecology, pediatrics, child psychiatry, and other areas will continue to be major targets of this Institute's training support during 1968.

Reproduction, Population, and Perinatal and Infant Mortality.—For the remainder of 1967 and 1968, funds will be used to stimulate research training in areas pertinent to furthering knowledge of the reproductive processes and the understanding of population problems. Specifically, training for obstetricians, gynecologists, physiologists, biologists, and endocrinologists will be emphasized. Population problems will necessitate training competent scientists to study fertility regulation, population dynamics and the sociological and psychological aspects of reproduction. Emphasis will also be given to training the researchers necessary to find new ways to combat perinatal and infant mortality and morbidity, including basic researchers and clinical investigators in such areas as pediatrics and developmental pharmacology.

Growth and Development.—During 1968, efforts to increase the number of scientists studying both the physiological and psychological development of children will be continued. Training will be supported in such areas as nutrition, pediatrics, development biology, physiology, genetics, neurology, sociology, child psychiatry and psychology.

Adult Development and Aging.—Training of scientists to conduct research in cellular biology, molecular biology, physiology, and psychology, as these relate to understanding of the aging process, will continue to receive emphasis during 1968. Support of research training concerned with the social and psychological problems of older citizens will be emphasized. Training will also be encouraged in areas of intramural interest to aid in staffing the new gerontology building in Baltimore.

Mental Retardation.—The needs of some 12 mental retardation research centers throughout the country emphasize the critical problem of training new scientists to staff these facilities. It is estimated that as these centers become operational they will require 1,000 new scientists. During 1968, funds will be used for training in the various biological, psychological, sociological and other fields necessary to further research efforts against mental retardation. Areas of training support will include pediatrics, neurology, cytogenetics, sociology, child psychiatry, and psychology to name only a new.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	111	$7,165,000	127	$8,360,000	+16	+$1,195,000
(b) Competing	10	816,000	9	693,000	−1	−123,000
2. Supplementals	(11)	151,000	(11)	151,000	(0)	0
3. New	20	1,387,000	7	458,000	−13	−929,000
4. Scientific evaluation	(3)	100,000	(3)	100,000	(0)	0
5. Total training grants	141	9,619,000	143	9,762,000	+2	+143,000

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Graduate	141	$9,519,000	143	$9,662,000	+2	+$143,000
2. Scientific evaluation	(3)	100,000	(3)	100,000	(0)	0
3. Total training grants	141	9,619,000	143,	9,762,000	+2	+143,000

Program analysis

	1967 estimate	1968 estimate	Decrease or increase
Reproduction	$3,898,000	$3,933,000	+$35,000
Growth and development	2,881,000	2,906,000	+25,000
Aging	1,450,000	1,465,000	+15,000
Mental retardation	1,290,000	1,358,000	+68,000
Subtotal, regular program	9,519,000	9,662,000	+143,000
Scientific evaluation	100,000	100,000	0
Total training grants	9,619,000	9,762,000	+143,000

Direct Operations

Laboratory and Clinical Research

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	200	$1,562,000	261	$1,904,000	+61	+$342,000
Other expenses		3,695,000		3,838,000		+143,000
Total	200	5,257,000	261	5,742,000	+61	+485,000

Introduction

This activity includes laboratory and clinical research in reproduction, growth and development, aging, and mental retardation. Laboratory studies currently underway are in the areas of basic reproductive biology and ecology, biomedical and behavioral aspects of mental retardation, diagnosis and clinical studies of the retarded, and gerontology research using both humans and animals at the Gerontology Branch in Baltimore and in Bethesda.

The funds requested for laboratory and clinical research represent a net increase of $485,000 in 1968 over 1967. A program increase of $739,000 is included which is partially offset by a decrease of $500,000 representing a non-recurring expense during the remainder of 1967 for the purchase of specialized equipment to be installed in the new gerontology building. Also included is an increase of $211,000 for centrally furnished services from the National Institutes of Health management fund, and a net increase of $35,000 for mandatory items such as annualization of positions new in 1967, offset by one day less pay in 1968.

Program plans for 1967 and 1968

Reproduction, Population, and Perinatal and Infant Mortality.—This program's intramural activity is centered in laboratories in the Clinical Center where scientists are concentrating on problems relating to conception, gestation, relationships between the anterior-adrenal-reproductive systems, and the role of biotin, a crystalline growth vitamin of the vitamin B complex, and other factors in reproductive physiology.

Other studies underway in this laboratory include systematic, quantitative investigations of hormone production and secretion throughout pregnancy and the menstrual cycle in rhesus monkeys, studies of ovarian function in monkeys and other pregnant animals, steroid hormone metabolism studies in pregnant monkeys, and research on the nature and effects of fetal hormones in both fetal rabbits and pigs.

During the remainder of 1967 and in 1968, these intramural researchers will continue current research efforts and initiate studies relating to implantation and placenta formation in monkeys and other animals. Elucidation of basic reproduction through the studies conducted in this laboratory and in other institutions is expected to aid in preventing pregnancy-related problems and supply valuable knowledge for use in the development of safer and more efficient means of contraception.

Growth and Development.—Intramural research in this area includes nutritional studies dealing with carbohydrate metabolism and the combined effects of hormones on glucose (sugar) metabolism. Current studies focus on liver function, the influence of hormones on key regulating enzymes, and the changes which occur during the developmental process. In addition, scientists are investigating learning environments of preschool children, characteristics of children from deprived environments, relationships between environment, and changes in these children's intellectual and personality characteristics, and interrelationships between cognitive and personality functions of preschool children. These studies are being carried out with subjects from the Washington, D.C. Head Start program.

For the rest of 1967 and in 1968 the Institute will expand its efforts to include studies in developmental biochemistry, developmental immunology, physical growth and developmental physiology including neurophysiology. The Head Start studies will continue, and it is expected that investigations will be initiated into the physiological correlates of behavior, cognition and learning, social development, and personality development.

Adult Development and Aging.—A major effort of the Aging Program is to bring to fruition the plans for its intramural research. Intramural research on aging has been carried out by the National Institutes of Health since 1941 when a research activity in that field was established at the Baltimore City Hospitals. This activity eventually became the Gerontology Branch of the National Heart Institute and in 1965 was transferred to the National Institute of Child Health and Human Development. The staff of this intramural research activity has grown from a few persons in 1941 to approximately 80 at present. Currently the research laboratories are in the Baltimore City Hospitals, but a separate Federal building is being constructed on the grounds adjacent to the hospital and will be complete in 1967. This building will provide space for a staff of approximately 300 persons working on many aspects of the aging process. Studies will be made at many levels of complexity ranging from molecular structure to social processes. The activities being carried out there will be expanded as rapidly as positions can be made available and staff can be recruited. This intramural program offers an opportunity for the direct support of work highly relevant to the aging process, at all levels of complexity, from the molecular to the sociological.

This building will provide a center for many kinds of research on aging. Not only will direct intramural research be carried out there but facilities will be available for collaborative research directed toward aging. This will be carried out with investigators from the Baltimore City Hospitals, the Johns Hopkins School of Medicine, and the University of Maryland School of Medicine. In addition, facilities will be available, for visiting scientists wishing to carry out research requiring the colonies of young and old animals that will be available there.

Mental Retardation.—This program is presently centered in the Children's Diagnostic and Study Unit at the National Naval Medical Center and in the Laboratory of Biomedical Sciences.

The Children's Diagnostic and Study Unit conducts clinical research and diagnosis utilizing patients eligible to receive care at the U.S. Naval Hospital. This unit also contributes case material for basic research in the biomedical and behavioral aspects of mental retardation. The clinic team has been conducting studies on effective diagnostic counseling techniques and on learning, motivation, and teaching as these relate to the mentally retarded. During 1968, efforts will be expanded to include research on improving attending behavior in preschool retardates, assessing behavior of neonates, free-play situation behavior, and operant conditioning audiometric techniques.

Institute scientists are also emphasizing studies in biochemistry, cytogenetics, and neurophysiology. During 1967 they have been working in borrowed space at the National Institutes of Health and the National Naval Medical Center. Additional space will soon be available at the National Naval Medical Center to consolidate most of this research in laboratory facilities located adjacent to the Children's Diagnostic and Study Unit.

Collaborative research and development

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	46	$391,000	46	$401,000		+$10,000
Other expenses		986,000		986,000		
Total	46	1,377,000	46	1,387,000		+10,000

Introduction

This activity serves the important purpose of supplementing and complementing our intramural 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 1967 and 1968

Of the $10,000 net increase, $7,000 will be used for scientific information centers in aging, growth and development, and reproductive biology.

The primary objective of these Centers is ultimately to provide a basis for critical interdisciplinary analyses of current research and future research needs in the program areas. Corollary to this is the provision to all the biomedical, social, and behavioral disciplines concerned with each of the program areas a ready access from a single source to past and current research and research-related services; formulated plans for future research, whether formally published in scientific journals or available through information progress reports; and a rapid identification of people and institutions working in any particular field.

A necessary base to both of these objectives is a compilation of information which is as complete as possible, wherever in the world it is available. With this information available, the researcher can move ahead confident that he has not missed any information that will help him in his research and with the assurance that he is not unnecessarily duplicating work already sufficiently performed. The practitioner will have available to him that research which is now and potentially ready for application and evaluation in the field.

The critical analyses will provide both the extramural research community and the Institute's intramural research program with identification of gap areas present in current research and with potential new research directions.

In 1967 material for the Information Centers in Aging, Growth, and Development and Reproductive Biology will be indexed and abstracted, and abstract journals published. It is expected that surveys on current research in Reproductive Biology will be ready for publication in 1967, and for the other two areas during the first part of 1968.

Included in the net increase is $5,000 for centrally furnished services from the "National Institutes of Health Management Fund" offset by a decrease of $2,000 for one less day of pay in 1968.

BIOMETRY, EPIDEMIOLOGY AND FIELD STUDIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	51	$423,000	51	$438,000		+$15,000
Other expenses		1,498,000		1,501,000		+3,000
Total	51	1,921,000	51	1,939,000		+18,000

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 requested net increase of $18,000 includes a $15,000 program increase, $5,000 for centrally furnished services from the "National Institutes of Health Management Fund", offset by a $2,000 decrease for one day less pay in 1968.

Program plans for 1967 and 1968

The need for sound epidemiologic and biometric studies in the area of reproduction is particularly great. One of the epidemiological projects currently being conducted is a study of the characteristics of the human menstrual cycle. University affiliated 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. In 1966, the Institute contracted to support this research. 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 menstrual experience data which has been gathered as a result of this study is perhaps the largest and most comprehensive in the world. The analyses resulting from this data will be a major resource to all studies concerned with menstruation. Computer methodology is currently being used to find the most efficient ways of recording, storing, and retrieving the mass of information for fast and easy reference.

In 1967, studies of the menstrual cycles and pregnancies of Eskimo women will be initiated. These will provide data comparable to the data in the long-range study mentioned above, and will help science assess environmental, cultural, and behavioral influences in the reproductive processes.

Another important behavioral study currently being conducted is a survey of family planning practices in the United States. This is the third of a series of surveys, the first two having been conducted in 1955 and 1960. Not only does the study provide data comparable to the 1955 and 1960 studies for measuring family planning and fertility trends over a period of years, but it also provides vital information on use of oral contraceptives according to race, religion, family size, education, age, and socio-economic levels. In addition to collecting statistics about past, present, and future use of the oral contraceptives, the survey includes sources of family planning information and other birth control methods used. Analysis of these data will continue in 1967, providing up-to-date and comprehensive information concerning the social and psychological aspects of family planning—an area of great importance in reproduction and population studies.

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. Within the next year, the use of food supplements will be started within the villages studied. The project is expected to extend over a number of years to permit evaluation of the long-term effects of dietary improvement.

The Institute is supporting a cooperative study by several western states to collect epidemiologic information on the children residing in institutions for the mentally retarded. The survey is particularly designed to assess the handicapping conditions present in these children, with the goal of developing knowledge which will lead to better methods of caring for their medical and psychological needs.

Training Activities

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	5	$43,000	5	$44,000		+$1,000
Other expenses		47,000		47,000		
Total	5	90,000	5	91,000		+1,000

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. The program increase of $1,000 will provide for the increased costs of supporting this training.

Review and Approval of Grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	83	$763,000	84	$793,000	+1	+$30,000
Other expenses		927,000		993,000		+66,000
Total	83	1,690,000	84	1,786,000	+1	+96,000

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 Council; required Council staff assistance; liaison with 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.

Included in the $96,000 net increase is a program increase of $44,000 which will be used to meet increased staff costs due to the added workload in the grant areas. In addition, there is an increase of $3,000 for one day less pay in 1968. There are also increases of $52,000 for centrally furnished services from the "National Institutes of Health Management Fund".

Program Direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	45	$445,000	46	$461,000	+1	+$16,000
Other expenses		369,000		420,000		+51,000
Total	45	814,000	46	881,000	+1	+67,000

This activity includes the Offices of the Director, Associate Director for Planning and Evaluation, Executive Officer, Administrative Officer, Budget Officer, and their supporting staffs including clerical staff for the Personnel 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 $67,000 net increase request for program direction includes a program increase of $50,000 to continue effective management of a growing organization, $19,000 for centrally furnished services from the "National Institutes of Health Management Fund"; offset by a $2,000 decrease for one day less pay in 1968.

New positions requested in 1968

	Grade	Annual salary
Laboratory and clinical research:		
Medical officer	GS-15	$17,550
Scientist administrator	GS-15	17,550
Scientist administrator (2)	GS-14	30,212
Psychologist	GS-13	12,873
Geneticist	GS-13	12,873
Chemist	GS-13	12,873
Biochemist (2)	GS-12	21,854
Biologist	GS-12	10,927
Do	GS-11	9,221
Chemist (2)	GS-11	18,442
Administrative assistant	GS-11	9,221
Research technician (2)	GS-9	15,392
Chemist	GS-9	7,696
Public health nurse	GS-8	7,068
Biomedical laboratory technician	GS-8	7,068
Biology laboratory technician (2)	GS-7	12,902
Biologist (3)	GS-7	19,353
Social science analyst	GS-7	6,451
Chemist (2)	GS-7	12,902
Purchasing agent	GS-6	5,867
Physical science technician	GS-6	5,867
Secretary (2)	GS-5	10,662
Laboratory technician (3)	GS-5	15,993
Chemist	GS-5	5,331
Medical technician (2)	GS-5	10,662
Clerk typist (2)	GS-4	9,552
Medical technician (2)	GS-4	9,552
Supply clerk	GS-4	4,776
Clerk typist (2)	GS-3	8,538
Animal caretaker	GS-3	4,269
Laboratory worker	GS-3	4,269
Laboratory helper (2)	GS-2	7,850
Director grade (2)	CO	32,520
Senior grade (3)	CO	38,160
Full grade (6)	CO	57,939
Senior assistant grade (2)	CO	15,964
Total (61)		510,199
Review and approval: Medical officer (1)	GS-15	17,550
Program direction: Administrative officer (1)	GS-12	10,927
Total new positions, all activities (63)		538,676

WEDNESDAY, APRIL 12, 1967.

DIVISION OF ENVIRONMENTAL HEALTH SERVICES

WITNESSES

DR. PAUL KOTIN, DIRECTOR, DIVISION OF ENVIRONMENTAL HEALTH SCIENCES
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. SAMUEL S. HERMAN, ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH, DIVISION OF ENVIRONMENTAL HEALTH SCIENCES
GEORGE M. KINGMAN, ACTING EXECUTIVE OFFICER, DIVISION OF ENVIRONMENTAL HEALTH SCIENCES
ROBERT H. BRAMLET, BUDGET OFFICER, DIVISION OF ENVIRONMENTAL HEALTH SCIENCES
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.0	Permanent positions	185	436	1,572
11.3	Positions other than permanent	4	3	10
11.5	Other personnel compensation	3	1	2
	Total personnel compensation	192	440	1,584
12.0	Personnel benefits	25	37	148
21.0	Travel and transportation of persons	52	67	152
22.0	Transportation of things	4	53	73
23.0	Rent, communications, and utilities	20	208	253
24.0	Printing and reproduction	2	20	40
25.1	Other services	15	147	210
	Project contracts	134	250	537
25.2	Services of other agencies	41	21	2
25.3	Payment to: "National Institutes of Health management fund"	306	434	1,057
26.0	Supplies and materials	70	113	155
31.0	Equipment	304	212	438
41.0	Grants, subsidies, and contributions	7,759	11,320	15,966
99.0	Total obligations	8,924	13,322	20,615

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	52	56	176
Full-time equivalent of other positions			1
Average number of all employees	29	52	165
Average GS grade	8.2	8.8	8.8
Average GS salary	$8,716	$9,403	$9,403

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	5,001	7,016	10,421
(b) Training	2,758	4,304	5,545
2. Direct operations:			
(a) Research	861	1,506	4,075
(b) Review and approval of grants	162	301	356
(c) Program direction	117	195	218
3. Adjustment of prior year costs	—1,444		
Total program costs, funded [1]	7,455	13,322	20,615
Change in selected resources [2]	—1,469		
10 Total obligations	8,924	13,322	20,615
Financing:			
16 Comparative transfers to other accounts	6,801	10,752	
25 Unobligated balance lapsing	247	224	
New obligational authority	15,972	24,298	20,615
New obligational authority:			
40 Appropriation	15,983	24,298	20,615
41 Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (79 Stat. 531)	—3		
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	—8		
43 Appropriation (adjusted)	15,972	24,298	20,615
Relation of obligations to expenditures:			
10 Total obligations	8,924	13,322	20,615
70 Receipts and other offsets (items 11–17)	6,801	10,752	
71 Obligations affecting expenditures	15,725	24,074	20,615
72 Obligated balance, start of year	6,270	12,392	19,368
74 Obligated balance, end of year	—12,392	—19,368	—22,264
77 Adjustments in expired accounts	—92		
90 Expenditures	9,511	17,098	17,719

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. We now have Dr. Paul Kotin, who is the Director of the Division of Environmental Health Sciences. We have a biographical sketch of Dr. Kotin which we will include in the record at this point.

(The information follows:)

Name: Paul Kotin, M.D.
Position: Director, Division of Environmental Health Sciences.
Birthplace and date: Chicago, Illinois, 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—present: Director, Division of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.

1966: Scientific Director for Etiology, National Cancer Institute, Bethesda, Maryland 20014.

1963–1965: Associate Director for Field Studies, National Cancer Institute, Bethesda, Maryland 20014.

1962–1963 (June): Chief, Carcinogenesis Studies Branch, National Cancer Institute, Bethesda, Maryland 20014.

1960–1962: Paul Peirce, Professor of Pathology, University of Southern California School of Medicine, Los Angeles.

1949–1959: University of Southern California School of Medicine.

1946–1948: Private practice in pathology and internal medicine, San Luis Obispo, California.

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 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, Gordon Research Conference on Cancer, 1965; Department of Health, Education, and Welfare, Superior Service Award, 1966; Dr. Kotin has authored and co-authored 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.

Mr. FLOOD. Doctor, you may proceed with your statement.

GENERAL STATEMENT

Dr. KOTIN. It is my privilege to appear before you on behalf of the newly created Division of Environmental Health Sciences. Since this is the first time an appropriation request has been made for this organizational unit, I should like to give you some of the background leading to establishment of the Division.

ORIGIN OF INSTITUTE

The well-being of man is intimately linked with his environment. The complexity of the environment and the ways that it can influence man's health have been greatly enlarged as a result of population growth, urbanization, industrialization, and the multiplying use of chemical substances. The once prominent problems of communicable disease have declined in urgency. In their stead we are now faced with problems related to contamination of our environment that threaten the health and character, if not the very existence, of life forms. The rewards of a rapidly advancing technology are large, tangible, and immediate. The penalties to be paid for this progress are somewhat removed in time and less visible, but clearly unavoidable. There is little room for complacency in the notion that what doesn't show doesn't matter. It seems certain that unless we address ourselves forcefully to the health problems associated with our environment in this age of chemistry, we shall inevitably suffer from the very advances that we are making.

The growth of environmental contamination since the end of World War II has served to focus the attention of the Federal Government on this threat to health. Indeed, there is rising concern that environmental hazard, actual and potential, can not only generate adverse effects on the health of individuals, but under certain circumstances can affect large segments of our population. Such concern has been registered by several distinguished advisory groups which have called attention to the constantly changing patterns of environmental health problems and have recommended an expansion of research efforts in this field by the Public Health Service. In November 1961, for example, a Committee on Environmental Health Problems, under the chairmanship of Dr. Paul M. Gross, recommended to the Surgeon General the creation of a center, including a new Office of Environmental Health Sciences. Such an office, it was believed, would offer a new method for attacking those facets of environmental health prob-

lems that were common to many of the operational programs. Moreover, it would permit by its integrated approach an identification and appraisal of problems that were not yet under consideration.

Congress appropriated funds in 1965 for planning a central environmental health facility, which would be devoted to the type of study envisaged by the Gross committee. Following the recommendations of a site selection committee, the Secretary of Health, Education, and Welfare announced in January 1965 that the center would be located in the Research Triangle area of North Carolina. Advice on the mechanism for activating such an undertaking was subsequently obtained from a group drawn from the National Advisory Environmental Health Committee, headed by Dr. Detlev W. Bronk. This was followed in November 1965 by the report of a contract-supported study of plans for the center's mission, scientific components, facility requirements, and staffing needs.

The Division of Environmental Health Sciences was established as part of the National Institutes of Health on November 1, 1966. As approved by the Secretary of Health, Education, and Welfare, the Division is to encompass a program of direct laboratory research and field studies in the North Carolina facility to be designated as the National Environmental Health Sciences Center. Also to be included is a program of research and training grants to support non-Federal activity in relevant science areas and to sponsor the establishment of university centers for research and training. Program activities, including ongoing grant-supported projects, were transferred with the appropriate funds from the former Bureau of State Services to the new Division. The Division's headquarters and the functions of program direction and development have also been located in North Carolina. Staff responsible for administering the Division's extramural operations is located in Bethesda.

MISSION AND GOALS

Organization and program in environmental health have in the past been oriented along one of three axes: (1) the hazard, (2) the vehicle by which the hazard is transmitted, or (3) the particular population groups affected. These are generally not conducive to the types of long-range investigation now considered necessary to identify the consequences of interaction of biological systems with hostile chemical and physical agents in the environment. In this connection, the need is twofold. First, there must be vigorous and integrated study of all facets of environmental effects upon human health and productivity. Second, there is an overriding need to establish the basic information upon which realistic control measures can be devised and adjusted to continual changes in both the environment and the population.

Accordingly, I see our mission as being directed toward providing a scientific base on which other units of the Service, particularly the Bureau of Disease Prevention and Environmental Control, can effectively engage in surveillance, standard-setting, control, and enforcement activities. This will necessitate collaboration with other elements of the National Institutes of Health in joint programs. It will require, too, a high degree of cooperation with academic institutions in furthering understanding of the relationship of environment to

health and in stimulating recruitment and training of research personnel. Implicit also in the overall mission is the early establishment of a referral point for scientific information involving Federal, State, and local programs; research organizations; and individual investigators.

RESEARCH OBJECTIVES

Research objectives will be oriented toward determining the mechanism by which environmental agents produce deleterious effects in exposed persons and the circumstances that influence the expression of these effects. Interest will be focused upon the fundamental nature of the body's response to these agents, individually and collectively, and the ultimate consequences for health, longevity, and productivity. In addition, the program will be geared to investigate and identify the opportunities that such basic knowledge may offer for counteracting the effects, increasing individual tolerance, protecting unusually susceptible segments of the population, and delineating the most effective points at which to exercise control.

Environmental hazards are ubiquitous and present relatively new types of health problem. Harmful agents—actual and potential—impinge upon man in intermittent or continuous doses and generally in low concentrations that reach him in a variety of ways. It is the total and cumulative exposure of the individual to these environmental insults that is now recognized to be important, whether they reach him through air, water, food, or skin contamination. The situation is further complicated by the fact that the emergence of disease is frequently not identified clearly in a cause-and-effect relationship with individual environmental toxicants. A striking exception is the effect of betanaphthylamine in producing bladder cancer in dye industry workers.

Identification of causes is not limited to new agents. The substitution of one agent by another or the addition of another agent can create new complexity and new problems. The addition of nickel as well as lead to gasoline and the use of plastics or fibers as well as asbestos in insulating materials are cases in point. Furthermore, the toxic effects of certain chemicals are multiplied many times by the simultaneous presence of another substance—a synergistic effect.

ECONOMIC COST

The economic cost of these ill-defined debilities has never been satisfactorily determined, but it clearly includes the care of the prematurely disabled, the nonproductivity of the partially effective, the diversion of medical services from the treatment of less avoidable disease, and a general reduction of effective effort through constant interruption and replacement of personnel.

SOCIAL COST

A social cost linked with less than optimum environments is the increasing public dissatisfaction with things as they are. Standards of acceptance are everywhere rising, with a corresponding increase in demand that something be done about the vague, chronic ill health that so long has come to be regarded as the inevitable lot of those past

middle age. The belief is developing that causes can be discovered and controlled and that the multiple, minor, and repeated environmental insults we have unwittingly brought upon ourselves are major contributors to this ill health, be it "bronchitis," "heart trouble," rheumatism," or plain "fatigue."

PROGRAM CONTENT

We are moving to attack these newer environmental health problems with a broad multidisciplinary approach and through use of multiple-program mechanisms. The provision of a cohesive framework for such activities will be a major objective of the Division.

The extramural program will provide funds for the support of research and training activities within educational institutions, research institutes, and other public and private nonprofit facilities. This will permit these facilities to play a key role in stimulating and expanding investigations in areas of relevance to the mission and goals of the Division. Support will be provided for research which ranges from small and circumscribed projects to broad and composite programs that integrate the research skills and efforts of investigators with diverse training. Grants administered by the Division have already made possible the establishment of university centers for research and training. These programs embrace numerous facets of environmental health research—clinical and nonclinical activity, rountine work and highly original studies, investigations by individuals and by teams, field studies, et cetera. The centers also permit advanced training in environmental health research in a depth and scope that are relatively unavailable elsewhere.

It is anticipated that extramural research will represent by far the major portion of the total national program in the area of environmental health. To this end the initial efforts of the senior staff of the Division have in significant measure been devoted to reviewing and establishing on a firm basis the ongoing and planned extramural research activities with emphasis on need, relevance, and pertinence as well as quality.

INTRAMURAL PROGRAM

In the intramural program, laboratory studies will be directed to duplicating circumstances of human exposure in experimental models, taking into account such factors as portal of entry, naturally occurring concentrations, time phasing of exposure sequences, and multiplicity of agents. Considerable attention will be directed to the long-neglected questions of the way in which agents operate together either in reinforcing or antagonistic fashion, the significance of dosage rate and frequency in relation to the total lifespan, and the deleterious effects of situations, such as that of smoking.

I believe that inattention to these problems would certainly lead to an increase in disability. This might become apparent in higher attack rates of cancer, cardiovascular, and pulmonary disease. Moreover, I would not be surprised to find that many of the factors associated with acceleration of chronic disease may be seen in retrospect to have been appreciably influenced by currently unrecognized factors in the environment.

The increase in sources of contamination, the introduction of numerous synthetic agents into the environment, and the growing recognition of the toxicity of certain natural products make individual bioassay of every possible agent manifestly impossible. It is essential, therefore, that we develop the principles on which the probable toxicity of new, as well as existing, contaminants can be predicted and appropriate measures taken.

ORGANIZATION AND STAFFING

One of the earliest needs has been to complete the administrative organization, the staffing pattern, and the advisory and liaison structure of the Division. We have succeeded to date in recruiting the key members of the scientific management team and support personnel. In addition, we have established a formal liaison mechanism between the Division and those units of the Service responsible for developing methods of control and protection from environmental hazards. This arrangement is for the purpose of acquainting the Division with operational problems on which further research is needed and making the other units aware of scientific information that is available for developing action programs.

Finally, an external advisory committee has been established to consult on general program and policy issues in the field of environmental health science. This group, which will have its initial meeting in May of 1967, will also conduct periodic review of the Division's intramural and extramural research programs and will advise on research priorities and allocation of resources.

SUMMARY OF BUDGET REQUEST

For these activities and the program which I have outlined, Mr. Chairman, we propose a budget of $20,615,000, an increase of $7.3 million over the $13.3 million available in 1967. The $20,615,000 includes $10,421,000 for research grants, $5,545,000 for training grants, and $4,649,000 for direct operations.

I shall be happy to answer any questions.

Mr. FLOOD. When was this Division formally created? What was the gestation period?

Dr. KOTIN. From conception to delivery——

Mr. FLOOD. Several years?

Dr. KOTIN. Many years. From the point of view of the neonate it has only been in business since November 1, when it became an integral unit of the National Institutes of Health.

Mr. FLOOD. Where are you located?

Dr. KOTIN. In the research triangle in North Carolina. This is an area of land dedicated——

Mr. FLOOD. I know where it is.

Dr. KOTIN. We do have at present some 25,000 square feet of space and plan to have an additional 30,000 square feet of research space available to us.

DELAY IN PLANS FOR MAIN FACILITY

Mr. FLOOD. You certainly have been dragging your feet on even planning the main facility. I don't mean you personally, I mean the Public Health Service. Certainly you have been dragging your feet on planning your main facility. This is what gets me off balance. You come in here asking for $7 million and the planning for the main facility hasn't even been completed yet.

Mr. KINGMAN. Of the $7 million Dr. Kotin is requesting for this activity, approximately $3.6 million is for increased cost of continuing research begun in preceding years.

At the research triangle he is requesting slightly less than $2.6 million for the intramural research activity. This, of course, is brand new and, as you point out, we have just begun down there.

Mr. FLOOD. Who do these buildings belong to? I show the witness now an exhibit of photographs of the triangle Center which he presented to the committee and there are buildings there with numbers on them. Now they do not belong to you?

Dr. KOTIN. They belong to the research triangle park. They are under lease to the Public Health Service and we occupy these facilities as research laboratories.

Mr. FLOOD. What happened to the plans, Doctor?

Dr. SHANNON. One of the reasons for the delay in the development program—I am talking in very broad general terms—was in obtaining scientific leadership. It was impossible to plan a program and recruit adequate personnel without the leadership. Quite frankly, we were rather loathe to ask Dr. Kotin to drop a very important area in the Cancer Institute—he was in charge of the carcinogenesis program. However, his general background is more broadly concerned with environmental health, and we felt that we would be better off if we could get very strong leadership accepting responsibility for running this——

Mr. FLOOD. What has that to do with plans for a main building?

Dr. SHANNON. The plans for program requirement for the permanent facility are in the process of development at the present time. Meanwhile, we have leased this amount of space with the commitment that the Center staff can have double that space by the end of the year.

Mr. FLOOD. What you are saying is very interesting but it is not responsive to the question: Why have the plans been delayed?

Dr. SHANNON. It was necessary to get scientific leadership.

Mr. FLOOD. I thought you had these fellows standing by. An hour ago you had scientists waiting to be hired. Do you mean you can't hire these scientists that are standing around?

Dr. SHANNON. Indeed; I think we can.

Mr. FLOOD. Why haven't you?

Dr. SHANNON. The urgency is great. We have the leadership and competence and capability now to engage suitable people for the endeavor that we would like to see come about. We would like to see this activity grow as fast as possible. This is the scientific base for the whole environmental health effort in the Public Health Service and it is long overdue. I do not think one can charge Dr. Kotin with foot-dragging——

Mr. FLOOD. I am not charging Dr. Kotin. When I said "you" that was entirely semantical. I mean the Public Health Service.

Dr. SHANNON. I think it has been an unfortunate experience, sir.

Mr. FLOOD. This is it?

Dr. SHANNON. I would just let it go at that. I think, on the other hand, we are ready to roll now. As part of the National Institutes of Health, this activity can grow, and grow very rapidly, under very strong leadership and deliver a very strong program.

RESEARCH GRANTS

Mr. FLOOD. Half of the increase is for research grants, Doctor. What type of research? What are you going to do?

CENTER GRANTS

In this description of your types of research you mention "center grants." What is a center grant?

Dr. KOTIN. A center grant is a grant made to a facility—usually a university—a medical school perhaps—for a purpose which has six or seven fundamental components in its conception. First, the centers develop in a pattern of diversity as an outgrowth of each individual university's particular interests. You identify at a given educational institution certain resources and strengths which are relevant to investigating problems in evironmental health. Then you fund these in a way that will utilize these resources on a multicategorical basis for the solution of certain problems which the facility and the members of the university already have manifested an interest in, by virtue of their past research efforts. In essence, the center grants represent an attempt to utilize the interests of key personnel in the university.

Second, the centers provide a focal point for treating the problem as it exists. Environmental health encompasses a complex reaction to a very complex environment. To investigate it on the basis of individual components of the enviroment—be they chemical or otherwise—to investigate it piecemeal on the basis of individual scientific disciplines would really be compartmentalizing an ambient situation which exists in nature as a totality.

The center permits you to attack a complex problem by the application of diverse and complex interdigitated mechanisms.

RESEARCH PROJECTS

Mr. FLOOD. You are going to fund more research projects. Tell us about them.

Dr. KOTIN. The research projects represent, as most research grant applications do, the interests of the scientists applying for support. The one overriding consideration in the support of projects is relevance to environmental health. There is a difference really analagous, I suppose, to that which exists between climbing the Matterhorn for its own sake or a view of the valley below or climbing it with a Geiger-counter attached to your belt. You can get to the top either way and the logistics of getting to the top is essentially the same but with the

Geiger-counter you can establish the presence of radioactive ore and determine whether it is worth mining, in addition to seeing the view.

If there is a hallmark of extramural support it is relevance to problems of environmental health.

Mr. FLOOD. Who thinks up the project? Are these your brain-children that you farm out or do people come in peddling them?

Dr. KOTIN. Some come in peddling, some we farm out. Our support in the area of individual project grants is not too dissimilar from the tradition that has evolved in the National Institutes of Health, with this one addition: I would reemphasize the importance of relevance to our mission.

TRAINING GRANTS

Mr. FLOOD. You have an increase of $1,241,000 for training grants. That will support an increase from 46 to 63 grants. In what fields are you going to train? There seems to be no horizon for your institute.

Dr. KOTIN. One of the things I think it is well to understand is that environmental health really does not have a discipline that is unique to it.

Mr. FLOOD. It certainly dosen't seem to have much discipline at all.

Dr. KOTIN. I have made my living through the years to employing a branch of medicine that really has no discipline of its own, but applies all the disciplines available to medical sciences. The training disciplines here would take the ongoing item of study and research and orient them to, identify them with and hopefully dedicate them to solving problems in environmental health. Thus the biochemist will be still trained as a biochemist but his training, research, and work will be concerned with problems in environmental health and this orientation will, hopefully, direct him to a career in this field.

Further than that——

Mr. FLOOD. Will this be postgraduate?

Dr. KOTIN. It will be both postgraduate and graduate training.

FELLOWSHIP PROGRAMS

Mr. FLOOD. It would appear you have missed something. All the other institutes have fellowship programs of some kind or another and you haven't. How did you miss that one?

Dr. KOTIN. I think the missing was probably in mentioning it. We do have a fellowship program. Again, the fellowship program is concerned with this overriding concern with training in areas relevant to problems in environmental health. What we are primarily interested in in the fellowship program is identifying scientists with great potential who can, in an area not necessarily limited to a center but wherever excellence may be——

Mr. FLOOD. May I interrupt. I bring your attention to page 315 of the justifications. I have marked there that I see no line item for fellowships. I have written that in, "no fellowships" and I wonder why, especially on a program like this.

Mr. KINGMAN. This structure which you see before you is essentially the structure of the program activity which we had transferred to the National Institutes of Health from what is now the Bureau of Disease Prevention and Environmental Control. They do not have a fellow-

ship program. In I believe January of this year, Dr. Kotin requested authority to establish a fellowship program from the Surgeon General. That was approved, and the Secretary's Office I think within the last 2 or 3 weeks, approved a reprograming of 1967 funds in the amount of a quarter of a million dollars, or $200,000. It was $200,000. So that going into 1967–68, we will be carrying a fellowship program at a level of $200,000 and admittedly it is not included in the budget which is before you.

Mr. FLOOD. What are you using for money?

Mr. KINGMAN. We requested permission for transfer of these funds from training grants to a fellowship activity.

Mr. CARDWELL. It is still within the broad category of support and assistance for training of manpower.

Mr. FLOOD. Isn't it nice I asked you? Otherwise nobody would have mentioned it.

Mr. KINGMAN. Sir, I was prepared to answer the question.

Mr. FLOOD. If I asked it.

Mr. KINGMAN. No, sir, I was prepared to testify.

DIRECT OPERATIONS

Mr. FLOOD. For direct operations in research you ask for $4,075,000 and 148 positions. This compares with $1,506,000 and 30 positions that you have this year.

Let me assure you, Doctor, that an increase of that magnitude right now is going to most certainly attract somebody's attention when we sit around this big table to mark up this bill.

What would happen if you did not get half of it, or any of it?

Dr. KOTIN. In the general sense, of course, if we did not get part of it, the number of programs planned by key personnel which are already on board would obviously have to be curtailed. What we have done is identify in the environment a whole series of areas in need of study and what we have tried to do is combine both the availability of skill, the national need, and the urgency of problems into an equation which gives us a pattern of program implementation. A sequence of program implementation, if you will. And what we would do in the case of a curtailment of resources is just not implement to the extent we would hope to and we feel the national need merits during the coming year.

Dr. SHANNON. It would just prolong the development of the activity and we feel the delay has already been unduly long.

Mr. CARDWELL. Mr. Chairman, I might emphasize that beginning with the Secretary's testimony and running through today, this committee has heard literally reams of testimony about problems of the environment. This testimony, it seems to me, adds up to the fact that we are falling farther and farther behind in the health aspects of our environment, and a delay would certainly impair this.

I would point out that about $16 million of the $20.6 million budget for 1968 is in grants and contracts and, as Dr. Shannon has pointed out, the university community and the nonprofit foundations and others who would engage in grants and contracts are ready to use the money to work toward solution of these problems.

TOBACCO AND HEALTH

Mr. NATCHER. I want to direct your attention to page 325 of your justifications where you state that special interest will be given to problem areas of tobacco and health, pesticides, heavy metals and trace elements, mycotoxins and other natural toxins, synthetic organic compounds, and other agents of environmental media which represent actual or potential health hazards.

What do you plan next year in the area of tobacco and health?

Dr. KOTIN. We plan to dedicate $480,000.

Mr. NATCHER. Next, pesticides, Dr. Kotin.

Dr. KOTIN. $640,000 including synergists.

Mr. NATCHER. Next, heavy metals and trace elements.

Dr. KOTIN. $320,000.

Mr. NATCHER. Mycotoxins and other natural toxins.

Dr. KOTIN. $160,000.

Mr. NATCHER. Synthetic organic compounds.

Dr. KOTIN. $320,000.

Mr. NATCHER. How about air pollutants?

Dr. KOTIN. The air pollutants really represent the environmental location of many of the groups of agents you have already mentioned.

We are concerned with metals: nickel, lead, cadmium, as substances in the air. We are concerned with hydrocarbons or synthetic chemicals as substances in the air. It really depends on how you want to break them down. If we broke them down into environmental sources we would still have the same list, If we broke them down on the basis of chemical characteristics they would be this way.

Or if we broke them down on, for instance, how they enter the body, either through the gastrointestinal, respiratory system, or through the skin, so potentially you have a number of matrices you can break down in any way you want to, depending on the approach you want to use.

SYNERGISTS

Mr. NATCHER. Doctor, do you have any other amounts designated that you contemplate using in other areas that I do not mention along this line?

Dr. KOTIN. Yes, sir.

Mr. NATCHER. Give those to the committee.

Dr. KOTIN. Yes, sir. There is a whole group of compounds that fall into the chemical category of synergists. These are compounds that are added to products, or industrial processes, or techniques for one of the purposes of reducing hazards where they have been identified. For example, pesticides have been shown at certain concentrations to be hazardous.

The industry in a very laudable manner began to study the possibility of reducing the concentration of the actual lethal agent in the pesticide by perhaps adding a nonlethal agent which would work in combination with it so it would get the same insecticide or pesticide effect with the lower concentration of the pesticide.

It so happens that many of these synergists are complex chemicals and on the basis of existing knowledge it was assumed many of them were completely innocuous. Specifically with certain pesticides, for instance, some of the synergists which by themselves are completely

innocuous in combination with the pesticide, if anything, not only enhance their toxicity but can adversely affect the response to agents present as air pollutants or constituents of entirely different environmental sources. We feel the whole area of synergists—because it really represents a trend and, as I say, an understandable trend on the part of industry—is one that we feel we can now attack in its infancy and perhaps identify in collaboration with industry, synergists that are less likely to have an unanticipated side hazard.

Secondly, we are in a position, we feel, to launch studies that take into account more than a single exposure to a single agent. I would judge the environmental health center really has as one of its major responsibilities the utilization of experimental models which try to, within the limits of technology, produce systems that represent as nearly as possible the human situation. Under normal living conditions we are rarely exposed to a single agent.

A person drives home. He comes from perhaps a dusty occupation. He stops behind a bus which is emitting a fair amount of fumes and he comes home and there are many chemical agents that have been sprayed around the house to kill an insect, and so on. We really do not know what the effect of this multiple sequential exposure is. Indeed, the technology for investigating this, the laboratory model, requires a fair amount of development. I think at present we can move from the single exposure-single target experiment in the framework of a laboratory to studies of two agents, agents picked out of the environment that have immediate relevance to man. In some areas technologically we can handle three agents, a virus, a chemical, and perhaps ionizing radiation, or just groups of chemicals and expose models to all of these. The synergists fall into the area of enhancing agents which alone have been subjected to study and, indeed, are innocuous or they would not have been licensed, but in combination you have a different system through which the body targets respond in a different way.

Mr. NATCHER. Do you plan the funding of any other programs along this line?

Dr. KOTIN. This is really so all inclusive that I would be hard put to identify any programs that would not fit in under this general categorical approach.

PLANS FOR SYSTEMATIC RESEARCH PROGRAM

Mr. NATCHER. Has the division drawn up plans for a systematic research program with respect to any of these areas?

Dr. KOTIN. Yes, sir; we have.

Mr. NATCHER. Would you submit it with the permission of the chairman, to Mr. Moyer? Is it voluminous?

Dr. KOTIN. Since we do want to get off the ground and get off the ground rapidly, it is at the protocol level virtually, and I am sure this is probably considerably more detailed than the committee might be interested in.

Mr. NATCHER. Mr. Chairman, with your permission I would like for Dr. Kotin to submit to you and to Mr. Moyer for inspection prior to insertion in the record of a summary.

Dr. Kotin, we want to know in substance what you have in mind, but not anything voluminous.

Mr. FLOOD. Without objection, it will be placed in the record.
(The information follows:)

PRINCIPLES OF RESEARCH

In describing the research approach to the several areas listed earlier, certain principles are applicable to all and these serve as rigid and firm criteria and guidelines for the design of experimental protocols, the implementation of experimental procedures, and the interpretation of data. These are:

1. Identification and verification of the need for the study on the basis of national need. The components of this determination are: a. epidemiological evidence of an unusual risk or distribution of disease in the general population or any of its component segments, b. suspicion of a potential hazard by an agent already present in the environment either as a pollutant or commercial product or one intended for introduction, on the basis of chemical structure or physical properties of the agent, c. the identification or suspicion of toxicity or health hazard on the basis of a possible combination effect with other environmental agents despite the apparent nontoxicity of a given substance when exposure occurs to it alone.

2. Experimental studies will encompass the simultaneous application of: a. fundamental research approaches aimed at elucidating and identifying mechanisms of toxic effect and tissue response so that principles and generalizations for use in developing predictive bench marks for health hazards may be evolved, and b. exposures of the total host for bioassay studies under circumstances that technologically most nearly duplicate those of the human situation. The bioassay studies will take into account the unique susceptibility of the extremes of life (infancy and old age) as well as individuals with tissue injuries or physiologic deficiencies associated with antecedent or concurrent disease. The effect of toxic agents on the developing fetus will also be studied through the exposure of pregnant animals under laboratory conditions to study the hazard of congenital malformities. Experimental exposure will be at dose levels approximating those that occur ambiently. The effect of exposure to multiple agents will be tested in a manner that will measure the effect of one upon another as well as on the host. The choice of agents for combined or multiple exposure study will take into account the human situation.

3. The selection of animal species for study is gradually progressing from one of empirical choice on the basis of laboratory considerations, to one of selection on the basis of expanding knowledge of comparative pharmacology. For certain agents, man is indeed a mouse from a metabolic viewpoint; for others, a dog; and for still others, a subhuman primate. The choice of species will be made on the basis of the most recent advances in the area of comparative biology, and further fundamental studies increasing our knowledge in this area are contemplated.

4. Inherent in all studies will be the determination of the applicability of the concept of a. threshold of response, i.e. is there a level below which even the most toxic of agents will not produce either a short term or a long term hazardous effect and b. body burden, i.e. does a host with environmental chemical agents (pesticides, trace metals) stored or accumulated in his body react differently and from an altered base line when compared with a host free of body burden?

The above general criteria are integral of the several proposed studies described below and in the design of experimental approaches, they are constantly kept in view.

The proposed programs are presented in summary form.

TOBACCO AND HEALTH

Approaches to reducing the hazard associated with cigarette smoking can be arbitrarily divided into three main categories. (1) The preparation or formulation of a safer cigarette; (2) Identification of local tissue factors responsible for relative resistance or susceptibility to cigarette smoke as a base for attempts at host modification so as to protect or buffer the target systems against any hazardous constituents of cigarette smoke; and (3) Characterization of systemic metabolic patterns associated with relative resistance to cancer induction in general and cancer of the lung specifically.

It is now technically possible to remove or reduce certain constituents of cigarette smoke which have been incriminated as being responsible in part for the carcinogenic as well as the general toxic properties of cigarette smoke. A

listing of the agents is in the record. Efforts will be made to remove carcinogenic agents, cocarcinogens, irritants, pesticide residues and other potentially toxic agents either through preventing their introduction or formation, or through destruction or neutralization after formation. These studies will include an assessment of the contribution of soil constituents, determination of the chemical properties of unburned leaf as a precursor source of hazardous compounds, and an analysis of the chemical, physical, and biological effects of the final product and its combustion products as consumed by the general population. The chemical approach is outlined in table 1.

TABLE 1: TECHNICAL CONSIDERATIONS TOWARDS THE PRODUCTION OF A "SAFER CIGARETTE"

A. Reduction of Total Smoke Condensate:
1. Mechanical filtration (in most common use now);
2. Tobacco selection;
3. Increase in porosity of cigarette paper;
4. Additives, which alter combustion temperature;
5. Variations in cigarette packing (as distinguished from packaging);
6. Tobacco extraction (to remove lipophilic materials) (with ligroin).

B. Reduction of Carcinogens in Smoke:
1. Selective filtration;
2. Selective reaction;
3. Elimination of precursors (extraction);
4. Tobacco curing modifications;
5. Change in combustion temperature;
6. Tobacco growing alterations (fertilizers, suckering agents, etc. (fungicides).

C. Reduction of Co-carcinogens in Smoke:
1. Selective filtration;
2. Selective reaction;
3. Tobacco curing modifications;
4. Tobacco selection;
5. Tobacco extraction (ethanol);
6. Additives.

D. Reduction of Irritants (Which Interfere with Muco-ciliary Function):
1. Selective filtration;
2. Alteration of humectants;
3. Modification of combustion.

E. Protection of Muco-ciliary Function by Pharmacologic Means:
1. Inhalation of parasympatheticomimetic agents as spray;
2. Inhalation of parasympatheticomimetic agents as part of cigarette;
3. Inhalation of mucolytic agent (acetylcysteine type of chemical).

Of particular interest is the approach described under E., the possibility of the addition of minute doses of pharmacological agents to neutralize the irritant effect for the preservation of normal ciliary action and physiologic mucus secretion. Existing techniques for physical filtration and chemical adsorption will be studied in addition to newly developed ones, including extraction of precursors, free radical quenching, the use of pesticides with short half-lives, and alterations in combustion properties will be studied.

Bioassay experiments will include exposure of appropriate animal species to aerosols of cigarette smoke alone and in combination with other environmental agents under controlled conditions. The effect of cigarette smoke and its individual constituents will also be studied on cell preparations, organ culture, isolated organ systems, and in other specifically designed models.

MYCOTOXINS AND OTHER NATURAL PRODUCTS

The contamination of crops by fungi is a potential source of potent toxic agents to those exposed during agriculture, manufacture, and consumer utilization of products. Studies have been successfully pursued identifying one species of fungus which contaminates grains and other crops with a metabolic product that is the most potent carcinogen known. Techniques for the identification and control of fungi and fungal products which are potentially hazardous to humans are under investigation in collaboration with the Department of Agriculture. Both field and laboratory studies must be undertaken for the purpose of seeking out fungi and other microbiological contaminants possibly related to toxicity observed in certain population groups.

Certain plants and plant products contain toxic agents which produce their effect at a subthreshold level as measured by immediate response, however, following a long period of exposure, signs of liver toxicity and kidney toxicity become manifest. These will also be studied particularly to determine possible combined enhanced effects with other environmental agents. Finally these natural products will be investigated to measure the extent to which they interfere with normal detoxification mechanisms necessary to inactivate toxic agents entering the body from unrelated environmental sources. Analytical procedures will be directed to isolating the specific agent or agents responsible for toxicity and bioassay studies will be performed using exposure doses approximately those occurring naturally and when feasible in combination with other agents likely to be present in the environment at the same time. The mechanisms of toxicity will be studied at the cellular level as the requisite base for providing guidance to control. Mycotoxins and other natural products will be administered in the diet and by injection in appropriately designed protocols to assure maximum extrapolation to man.

TRACE METALS

Expose to metals in the general environment occurs to exceedingly low concentration, however, metals can be stored in the body for prolonged periods of time up to decades. We are faced with a situation in which trace amounts of certain metals are indispensable to life, while larger amounts can be toxic or lethal. As these metals are toxic agents in concentration above those usually taken in in a balance diet for example and in addition to producing acute and chronic toxic effects on their own, depending on dose, they can poison enzymes systems and other vital metabolic pathways so that presumed safe doses of other environmental agents including pharmaceuticals as well as contaminants of air, water, and food can exert an unanticipated toxic effect. The laboratory approach will include the basic studies on the mechanisms of metal complexing within the cell and with tissue constituents, transport of metals across membranes, and the effect of metals when present as part of an abnormal body burden or on the metabolism of other exogenous agents. Exposure will be by feeding, aerosol inhalation, and injection.

PESTICIDES

This is a generic term from several groups of compounds some of which have a toxic affinity for the liver; others for the kidneys; others for the circulating blood cells; and still others for the central nervous system. Many of the pesticides are instantaneous in their toxic effect at given concentrations; others require a longer period of time to manfest their adverse effect. In addition, some are rapidly destroyed while others are stored in the body for long periods of time. Finally, many pesticides act in a conjoint manner so that their effect may be additive, in certain instances synergistic, and at times even antagonistic. Laboratory models have been and are continuing to be developed which will permit the study of these agents in a way that will permit the determination of their effect at low levels over long periods of intermittent and sequential exposure alone and in combination. The effect of pesticides of the various classes will be studied from the most fundamental aspect at the cellular level to exposure of a wide spectrum of animal species in feeding, inhalation exposure, skin application, and injection. In common with all other toxicity studies, exposures will be for prolonged periods to low concentrations of the agents.

SYNTHETIC ORGANIC COMPOUNDS

The spectacular advances in synthetic chemistry have resulted in the widespread introduction of synthetic agents into all segments of the environment. Pharmaceuticals are less and less derived from natural sources. Food additives, preservatives, and emulsifying agents are primarily creations of laboratory chemistry. Synthetic agents are the bases for the newer pesticides, fibers, building materials, as well as prostheses used for the replacement or reinforcement of body tissues (artificial joints, bone grafts, arterial grafts, synthetic valves, etc.). The physical properties, chemical nature, and reactivity of many of these synthetics warrants their suspicion as potential hazards to those exposed to them during manufacture, distribution, or use. We propose to study selected ones where existing knowledge suggests a hazard. Inhalation and implantation techniques will be used.

CONSTITUENTS OF CIGARETTE SMOKE KNOWN AS CAUSE OF HUMAN DISEASE

Mr. NATCHER. Dr Kotin, can you show me any research study that pinpoints a specific constituent of cigarette smoke or tobacco smoke as the known cause of any human disease?

Dr. KOTIN. I believe I can, sir.

Mr. NATCHER. All right, go right ahead, Dr. Kotin.

Dr. KOTIN. In cigarette smoke there is a group of compounds known as polycyclic hydrocarbons. In occupational exposures to these hydrocarbons where the exposure is many, many, many times the ordinary that one is exposed to in cigarettte smoking, there is an increased risk to the development of cancer of various types.

If, for example, the skin is occupationally exposed to these things, the risk of skin cancer is increased.

Industrial hygiene procedures which have resulted in the elimination of this exposure have been accompanied by reduction or in some instances total elimination of the cancer risk.

Similarly in certain occupational exposures to hydrocarbons there have been increased risks to the developmentof lung cancer.

Again, the institution of industrial hygiene procedures which resulted in the elimination of these hydrocarbons has been accompanied by a reduction in the risk on the part of those occupationally exposed.

EPIDEMIOLOGICAL STUDIES ON CAUSES OF CERTAIN HUMAN CANCERS

Mr. NATCHER. Dr. Kotin, can you pinpoint this for me by pointing out any one research study that bears this out?

Could you put something right here in the record on that?

Dr. KOTIN. The epidemological studies which are research studies fully as well controlled as laboratory studies, I think document these well. I would be happy to supply for the record a bibliography of studies reporting just what I mentioned a few moments ago.

Mr. NATCHER. Mr. Chairman, I would like to have that submitted to Mr. Moyer. I do not want it voluminous, Dr. Kotin. Perhaps that can be inserted, Mr. Chairman, with your permission.

Mr. FLOOD. Without objection, it will be inserted.

(The information follows:)

The occupational environment has served as the most fruitful source of information establishing the role of environmental agents in the causation of certain human cancers. The introduction of protective measures to reduce or eliminate exposure in occupations with high cancer risk has resulted in most instances in a reduction or elimination in the increased incidence of cancer. Despite our present ignorance of the intracellular mechanisms specifically responsible for the transformation of a normal cell into a cancer cell this sequence of hazard—control—reduction of hazard—establishes a cause and effect relation on the operational level at the very least. The three major sites of occupational cancer are: cancer of the skin, cancer of the urinary bladder and cancer of the lung.

Cancer of the skin was the first occupational cancer described. In 1775 the connection between cancer of the skin of the scrotum and the occupation of chimney sweeping was reported. More recently there has been statistical demonstration of skin cancer as an occupational hazard in workers exposed to certain types of oils, waxes and tars. The chemical nature of the cancer inducing agents in these tars, oil, etc. has been established and tumors in animals have resulted from their administration. Industrial control measures instituted include effective and rigorous frequent medical examinations of workers who come in contact with oils and allied substances and provision of facilities for the encouragement of the use of high standard of personal hygene. A second approach has been the automa-

tion of industrial procedures where feasible, or the construction of "hazard containment" facilities within plants so as to asusre minimal exposure.

The first indication that tumors of the urinary bladder might in some instances be associated with occupation was made in 1895 when a surgeon noted that a number of men with bladder cancer under treatment in his urological clinic came from one factory that manufactured magenta. From that time reports of occupational bladder cancer have come from every country having a dye industry. Workers exposed to benzidine and beta naphthylamine were shown to be at maximum risk. Subsequent laboratory research resulted in the production of urinary bladder tumors in experimental animals with these two compounds.

Efforts were made to safeguard workers and when it was found in certain instances that protection was technologically impossible, the manufacture of these compounds was halted in several countries, including Germany, Switzerland and Great Britain. The cessation of manufacturers was accompanied by a significant reduction in the incidence of bladder cancer.

Occupational cancer of the lung was first observed in those occupationally exposed to radioactive ores during mining. It is of interest that an increased risk to lung cancer has been observed in miners of radioactive ores in the Colorado plateau of the United States. Of major interest to us are those occupational lung cancers caused by exposure to chemical agents similar to those present in cigarette smoke and polluted urban air. Specifically, high lung cancer risks have been identified in workers exposed to hydrocarbon fumes and gases in coking operations as well as workers exposed during the manufacture of gas from solid fuels. Several times the expected rate of lung cancer was observed in gas stokers and coke oven workers. In those industries where protective measures have been instituted, it has been shown that a reduction in the risk has paralleled the reduction in the occupational exposure. In several countries protective measures have not been instituted and the increased risk has either remained static or grown.

Chromium refining and processing is yet another industry where an increased risk to lung cancer was noted in those occupationally exposed. However, since the introduction of certain industrial protective measures, the risk to lung cancer has been significantly reduced.

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CIGARETTE TAR

Mr. NATCHER. What about tar, Dr. Kotin; has tar from cigarettes been shown to cause any human disease? A human disease now, Doctor.

Dr. KOTIN. Exposure to tar from cigarettes has been associated with increased risk to certain human beings; I think that is all we can say at present, in terms of the study of people. In terms of the study of the chemical components of tar. "Tar" is a generic term. Tar is not a specific entity. Tars differ. Three different tars would have three different chemical compositions, in terms of the substances in them and the amount of the substances, but certanly exposure to tars is manifested in the laboratory by the production in experimental models of certain diseases which are epidemiologically associated with an increased risk.

NICOTINE

Mr. NATCHER. Now, what about nicotine; has nicotine from smoke been shown to cause any human disease that you know of?

Dr. KOTIN. Within the framework of a "clean" experiment, as we say, I am unaware of any.

CAUSE OF LUNG CANCER

Mr. NATCHER. Dr. Kotin, do you yourself know of any established scientific fact as to the actual cause for lung cancer? Do you know of any scientific fact that points directly to the cause of lung cancer?

Dr. KOTIN. The cause on the basis of the interaction of a chemical agent with the cells, this we do not have. A cause in the sense that if you remove that agent from the environment you get a reduction in the risk, we do know about that, sir.

Mr. NATCHER. What particular study do you have in mind? More than one? One study, Dr. Kotin?

Dr. KOTIN. There are many, many studies in occupational environments where the removal of an environmental agent has been associated with a reduction in the risk, and I think this properly qualifies that agent as a causal one.

Mr. NATCHER. Which would you say would be the most important study that has been made along this line?

Dr. KOTIN. In my opening statement I mentioned the exposure of persons in the aromatic industry, to an aromatic chemical, beta-naphthylamine. Removal of this agent where it has been possible from the industrial environment has resulted in the actual disappearance of occupational bladder cancers, where controls are rigidly enforced and the demand for industrial hygiene is very great.

Mr. NATCHER. Doctor, as you well know, the National Cancer Institute is still searching for something in smoke that might cause lung cancer. I believe that is true, is it not? They are still searching, are they not?

Dr. KOTIN. They are supporting work and are engaged in work. I think "searching" carries with it a purposefulness that would not create the impression that they are searching for causes of lung cancer. I think the use of the phrase "cause of cancer" in any concept does a disservice to the actual initiation of a cancer. There is no one cancer caused by any one agent. Cancers are caused by a series of agents and frequently different agents acting in concert.

NATIONAL CENTER FOR ENVIRONMENTAL HEALTH

Mr. NATCHER. Dr. Kotin, in your answers to questions by our chairman and also in your general statement you discussed the sum that you are requesting for 1968 which will be used to set up and support university institutes for environmental health sciences.

Now, Dr. Kotin, tell us what the difference is and why we need both the university institutes and the national center. Why do you need both of them, Dr. Kotin?

Dr. KOTIN. I think the necessity for the center relates to the necessity for any broad program requiring a focal point. The individual institutes, as I indicated a moment ago, are being supported, identified on the basis of skills and interests that already exist in facilities, or in universities. There are certain universiteis that have great chemical skills around which the associated scientific disciplines relate. Others have great skills in physics, others in biology, and so on.

To utilize all of these skills to the maximum on a national effort I think requires a focal point which will identify the availability of these skills: More importantly, will identify areas that are being passed over by default where skills do not exist although the problem requires them. The center in a complementary manner can set about to develop these skills.

In other words, it is an attempt to have pieces of a jigsaw puzzle, when put together, make a picture. The individual components provide necessary and indispensable segments but the focal point for a national effort is very critical.

Mr. NATCHER. Dr. Kotin, where did the concept for a National Center for Environmental Health come from?

Dr. KOTIN. I think it was the consensus of people concerned with the effects of environment on people and people on the environment. Human diseases were appearing that were not explainable on the basis of traditional concepts. In the old days when you were exposed to a chemical agent, and even at present, in an occupational environment, you would not have to be professionally trained to know that people exposed to the fumes were getting sick and people not exposed were not getting sick. But we now know that responses are taking place at levels which do not produce immediate overt effects but do have long-range effects; effects which are adequate to alter body function so that we have a genuine concern for the response a month, a year, and a decade after an exposeure that does not produce an immediate response.

UNIVERSITY INSTITUTES

Mr. NATCHER. You now have seven university institutes?

Dr. KOTIN. In various stages, yes.

Mr. NATCHER. What do you mean by various stages?

Dr. KOTIN. In terms of support. Some are in the process of having their support reviewed by reviewing bodies. Some are actively pursuing research programs.

Mr. NATCHER. How many are actively pursuing research programs?

Dr. KOTIN. Three.

Mr. NATCHER. Three of the seven?

Dr. KOTIN. Yes.

Mr. NATCHER. That are in the advanced stage?

Dr. KOTIN. They are turning out data.

Mr. NATCHER. How many do you intend to establish?

Dr. KOTIN. We would like to establish 12 in terms of the first phase in our mission of environmental health centers and these, again, would have the capability of institutes as they meet the national need.

Mr. NATCHER. Thank you.

Mr. FLOOD. Mr. Smith.

Mr. SMITH. No questions.

Mr. FLOOD. Mr. Hull.

BALANCED PROGRAM FOR ENVIRONMENTAL HEALTH

Mr. HULL. Dr. Kotin, I want to ask you just a few questions about how you plan to distribute your research efforts. I believe that tobacco and health is just one aspect of your overall program which, as I understand it, extends to many other areas of environmental health. I hope to follow the progress of your Division because I think it is important to determine how many different things in the ordinary human environment may threaten people's health.

I certainly am not criticizing your interest in tobacco. I just want to be sure that it does not overshadow any of the other areas, and

I will be interested in seeing how your new Division applies its resources to learn more about the various things that have been mentioned in your budget request as areas for investigation and other things that may develop as worthy of investigation.

Is it correct that your program for research in the environmental health field will extend to all environmental health scientific areas?

Dr. KOTIN. Yes.

Mr. HULL. I believe you told Mr. Natcher what your areas of investigation are.

Dr. KOTIN. Yes.

Mr. HULL. Will you do this work in your Division or through grants?

Dr. KOTIN. Both, sir.

Mr. HULL. I believe you have described generally the programs involved. Which ones will receive special emphasis?

Dr. KOTIN. I do not know if at this stage of the game one can identify any that will receive special emphasis. I think many things go into determining what we will emphasize. The availability of technological knowledge for special programs will probably result in such programs being developed sooner than where we have to develop methodology, but the agents that represent potential hazards are such they are all in need of investigation. The six or seven I mentioned represent a distillate of many, many times that. I would say all are receiving equal emphasis.

Mr. HULL. Then none of these other areas will be neglected?

Dr. KOTIN. No.

INVESTIGATIONS IN SMOKING AND HEALTH

Mr. HULL. Briefly, what will any investigation regarding smoking and health seek to determine?

Dr. KOTIN. First of all it will attempt to identify in a quantitative way not only the components of cigarette smoke but the interrelationship of these components to one another, and the combustion characteristics that tend to produce one type of component more than another type. It will concern itself with techniques for altering the condensate along lines that will reduce the quantitative presence of known agents. Along this line we would concern ourselves with the mechanism for the generation of cigarette smoke and attempt to identify and modify those qualities which would appear to present a hazard following exposure to them. Biological studies will parallel and complement these analytical studies.

Mr. HULL. Will you be proceeding from predetermined conclusions in any particular area, such as smoking?

Dr. KOTIN. The only conclusions I would be proceeding from would be those my associates and I have reached from working in the field. I have worked in the field of cancer causation for many years. The primary target to me has been the lung, and I have devoted my efforts predominantly in terms of the effects of air pollution, which reflects my residence in Los Angeles for 12 years. But we will attempt to take a total approach.

Mr. HULL. Is not the first aim to determine whether a given substance is a threat rather than simply to assume that it is?

Dr. KOTIN. Naturally, and where the evidence is not adequate to assure this, we will attempt to verify it. I am sorry I did not mention this before but this is so fundamental to any approach that I did not mention it. You accept only that which satisfies the criteria you demand when you are performing an experiment.

BUDGET ESTIMATES FOR VARIOUS AREAS OF INVESTIGATION

Mr. HULL. Are you set up to keep track of the amount spent with respect to each area in which you are interested?

Dr. KOTIN. We propose to, yes.

Mr. HULL. How will you do this?

Dr. KOTIN. There has to be a large fudge factor in this, of course. The problem of hydrocarbons relates to emissions from vehicular exhausts, cigarette smoke, many products that are hydrocarbon in origin, and a person working on hydrocarbon toxicity will concern himself with all sources. I do not think we can necessarily confine it to the four I mentioned previously. The work, I think, will segregate itself in terms of efforts and all I can do is trade on experience.

Mr. HULL. Does the committee have your estimates of cost as to each area to be investigated?

Dr. KOTIN. I believe that has been made a part of the record, yes.

TOLEDANO ARTICLE ON CIGARETTES AND HEALTH

Mr. HULL. I have an article here that perhaps you are familiar with. It is entitled "Cigarettes and Health" by Ralph de Toledano. It concerns a Washington press conference by Lloyd Mallan, a distinguished writer and researcher of scientific subjects, and Dr. William B. Ober, director of laboratories at New York's Knickerbocker Hospital and professor of pathology at the New York Medical College.

Is Dr. Ober, in your opinion, a highly respected and competent physician and pathologist?

Dr. KOTIN. I really am not prepared to say.

Mr. HULL. Dr. Shannon, can you answer that?

Dr. SHANNON. I do not know him, sir. We will be very glad to find out about him.

Mr. HULL. If I may I would like, Mr. Chairman, to insert this article in the record at this point.

Mr. FLOOD. Without objection it is so ordered.

(The article referred to follows:)

CIGARETTES AND HEALTH

(By Ralph de Toledano)

A Washington press conference is frequently an exercise in futility. Reporters show up—some because they are assigned, some because they are interested, and almost all of them hopeful that drinks will be served. Questions are asked, with varying degrees of interest and hostility. Then the reporters leave with a bunch of handouts, and a few of them write stories.

This was roughly the pattern when Lloyd Mallan, a distinguished writer and researcher of scientific subjects, and Dr. William B. Ober, director of laboratories at New York's Knickerbocker Hospital and professor of pathology at the New York Medical College, held a press conference here. Mr. Mallan had written a book called "It Is Safe to Smoke"—which he wanted to discuss with the press—and Dr. Ober had journeyed to Washington to urge the public to read this book.

Most reporters were interested in what Mr. Mallan and Doctor Ober had to say about the U.S. Surgeon General's Report on "Smoking and Health," a document they did not know was held in fairly low repute by an overwhelming majority of the medical authorities who testified at Senate hearings on the dangers of tobacco. One reporter, who tried to dominate the press conference, was out to prove that both Doctor Ober and Mr. Mallan were tools of the tobacco industry and motivated by greed or malevolence in their dissection of the Surgeon General's report.

It was a little frightening to watch this performance. Time after time, the arguments the reporter presented—they were hardly questions—were demolished by Doctor Ober or Mr. Mallan. This merely increased the reporter's hostility and failed to budge him from his preconceptions.

Yet neither Doctor Ober, a pathologist of high reputation who has done heavy research in the field of smoking, nor Mr. Mallan, a painstaking journalistic analyst of scientific data, had any ax to grind. They had several points to make. As a scientist, Doctor Ober condemned the Surgeon General's report as a collection of unrelated statistics pointing to unwarranted and unsupported conclusions. After careful study of the report, 39 of the 49 medical experts and statistical mathematicians who testified before the Senate committee disagreed strongly with the Surgeon General's "findings." Of the ten who agreed with it, one was the Surgeon General himself and two were associates in preparing the report.

Doctor Ober, who has conducted an uncounted number of autopsies, examined the lungs of smokers and non-smokers, then referred back to their life histories. He could detect no relationship between the condition of the lungs of smokers and non-smokers, though supporters of the Surgeon General's report have always insisted that damage to lung tissue by cigarette smoke is always visible under the microscope. The report asserted flatly that cigarette smoking "increases the risk of dying from chronic bronchitis," a statement which has puzzled doctors since no one dies of chronic bronchitis.

Mr. Mallan, while taking no sides in the question of the hazards of smoking unfiltered cigarettes, made one major contribution: From the medical experts—leading men in their fields—he learned that the danger in cigarette smoking, if danger it is, comes mainly from the gases produced in burning the tobacco or whatever—they are now making lettuce-leaf cigarettes—which paralyze the cilia of the cells in our air passages. These cilia sweep upward those particles of tar and other presumably carcinogic matter in cigarette smoke. As long as the cilia are healthy, most of these particles are kept out of the lungs.

It may be that smoking causes lung cancer, emphysema, and heart trouble. The Surgeon General did not prove it but by issuing a loaded report, he simply cut off important research in the field. Many people switched to cigars and pipes, but neither the Surgeon General nor the various societies standing by his side had done any real research in the effects of these cigarette substitutes.

Mr. HULL. The article states:

Doctor Ober, who has conducted an uncounted number of autopsies, examined the lungs of smokers and nonsmokers, then referred back to their life histories. He could detect no relationship between the condition of the lungs of smokers and non-smokers, though supporters of the the Surgeon General's report have always insisted that damage to lung tissues by cigarette smoke is always visible under the microscope.

Is that true?

Dr. KOTIN. Damage is visible under the microscope.

Mr. HULL. I am talking about cigarette smoke.

Dr. KOTIN. I, as a pathologist, cannot look at a lung and say damage to lung tissue is due to cigarette smoke.

Mr. HULL. You are a pathologist and you do not know Dr. Ober, director of laboratories at New York's Knickerbocker Hospital and professor of pathology at the New York Medical College?

Dr. KOTIN. I know him by name. I am in no position to judge his qualifications. There are thousands of pathologists.

Mr. HULL. The article continues:

> The report asserted flatly that cigarette smoking "increases the risk of dying from chronic bronchitis,".

Is that true?

Dr. KOTIN. I think chronic bronchitis can be a cause of death.

Mr. HULL. Not a cause but is it true people die from chronic bronchitis?

Dr. KOTIN. I would say it is a cause of death, yes.

Mr. HULL. Then the article winds up by saying:

> It may be that smoking causes lung cancer, emphysema, and heart trouble. The Surgeon General did not prove it but by issuing a loaded report, he simply cut off important research in the field. Many people switched to cigars and pipes, but neither the Surgeon General nor the various societies standing by his side had done any real research in the effects of these cigarette substitutes.

Is that a true statement?

Dr. KOTIN. I cannot vouch whether the Surgeon General——

Mr. HULL. Is it untrue?

Dr. KOTIN. Research has been done on the effects of cigarette smoking and pipe smoking, yes.

Mr. HULL. What about lettuce leaves?

Dr. KOTIN. As I understand, there is a laboratory investigating the smoking of lettuce leaves as a substitute for tobacco.

Mr. HULL. That is all.

Mr. FLOOD. Thank you, gentlemen.

We will meet tomorrow morning at 10 o'clock.

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JUSTIFICATION MATERIAL

Division of Environmental Health Sciences

Amounts available for obligation

	1967	1968
Appropriation	$24, 298, 000	$20, 615, 000
Comparative transfer within NIH accounts	+383, 000	
Comparative transfer to "Urban and industrial health"	−2, 408, 000	
Comparative transfer to "Communicable diseases"	−8, 727, 000	
Total	13, 546, 000	20, 615, 000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$7, 016, 000		$10, 421, 000		+$3, 405, 000
General research support grants				(719, 000)		(+719, 000)
Environmental Health Science Institute		(2, 500, 000)		(3, 500, 000)		(+1, 000, 000)
Training		4, 304, 000		5, 545, 000		+1, 241, 000
Direct operations:						
Laboratory and clinical research	30	1, 506, 000	148	4, 075, 000	+118	+2, 569, 000
Review and approval of grants	16	301, 000	18	356, 000	+2	+55, 000
Program direction	10	195, 000	10	218, 000		+23, 000
Total obligations	56	13, 322, 000	176	20, 615, 000	+120	+7, 293, 000
Unobligated balance, reserve		224, 000				−224, 000
Total, obligations and balance	56	13, 546, 000	176	20, 615, 000	+120	+7, 069, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	56	176	+120
Full time equivalent of all other positions		1	+1
Average number of all employees	52	165	+113
11 Personnel compensation:			
Permanent positions	$436, 000	$1, 572, 000	+$1, 136, 000
Positions other than permanent	3, 000	10, 000	+7, 000
Other personnel compensation	1, 000	2, 000	+1, 000
Total personnel compensation	440, 000	1, 584, 000	+1, 144, 000
12 Personnel benefits	37, 000	148, 000	+111, 000
21 Travel and transportation of persons	67, 000	152, 000	+85, 000
22 Transportation of things	53, 000	73, 000	+20, 000
23 Rent, communications, and utilities	208, 000	253, 000	+45, 000
24 Printing and reproduction	20, 000	40, 000	+20, 000
25 Other services	147, 000	210, 000	+63, 000
Project contracts	250, 000	537, 000	+287, 000
Services of other agencies	21, 000	2, 000	−19, 000
Payment to "National Institutes of Health management fund"	434, 000	1, 057, 000	+623, 000
26 Supplies and materials	113, 000	155, 000	+42, 000
31 Equipment	212, 000	438, 000	+226, 000
41 Grants, subsidies, and contributions	11, 320, 000	15, 966, 000	+4, 646, 000
Total obligations by object	13, 322, 000	20, 615, 000	+7, 293, 000

Summary of changes

1967 enacted appropriation	$24,298,000
Comparative transfer within NIH accounts	+383,000
Comparative transfer to "Urban and Industrial Health" (2,408,000) and "Communicable Diseases" (8,727,000)	−11,135,000
Unobligated balance, reserve	−224,000
1967 total estimated obligations	13,322,000
1968 estimated obligations	20,615,000
Total change	+7,293,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built-in:				
1. Annualization of new positions authorized in 1967				$50,000
B. Program:				
1. Research grants		$7,016,000		3,405,000
2. Training grants		4,304,000		1,241,000
3. Laboratory and clinical research	30	1,216,000	118	1,961,000
4. Review and approval of grants	16	219,000	2	28,000
5. Program direction		133,000		17,000
Total program increases			120	6,652,000
C. Payments to the "National Institutes of Health management fund" for centrally furnished services:				
1. Laboratory and clinical research		290,000		590,000
2. Review and approval		82,000		27,000
3. Program direction		62,000		6,000
Subtotal, management fund increases				623,000
Total increases			120	7,325,000
DECREASES				
A. Program:				
1 less day's pay				−2,000
Nonrecurring items for equipment				−30,000
Total decreases				−32,000
Total net changes requested			120	+7,293,000

EXPLANATION OF CHANGES

Research grants.—The program increase of $3,405,000 will provide $719,000 for general research support grants, $1,000,000 for the expansion of the research centers, and $1,686,000 for an estimated additional 19 research projects in 1968.

Training grants.—The increase of $1,241,000 will provide for the initiation of 17 new programs.

Laboratory and clinical research.—The increase of $1,961,000 and 118 positions will provide for additional staffing and completion of the nucleus for the permanent animal colony, as well as initiation of the first phases of research in basic and applied disciplines.

Review and approval of grants.—The increase of $28,000 provides 2 new positions and supporting services for the staff responsible for the review, processing and awarding of grants.

Program direction.—The increase of $17,000 will provide additional operating expense support for the Director of the Division and his staff.

AUTHORIZING LEGISLATION

The 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 encoruage, 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."

Explanation of transfers

	1967 estimate	1968 estimate	Purpose
Comparative transfer from: Other NIH accounts	$383,000		Redistribution of the National Institutes of Health Management Fund.
Comparative transfer to:			
Urban and industrial health	2,408,000		Transfers from parent appropriation following reorganization within PHS.
Communicable diseases	8,727,000		

EXTRAMURAL RESEARCH ACTIVITIES, FISCAL YEAR 1968 BUDGET REQUEST AND PROGRAM STATEMENTS

Program budget—Summary

Activity	1967 estimate	1968 estimate	Increase or decrease
Research grants and general research support	$7,016,000	$10,421,000	+$3,405,000
Training grants	4,304,000	5,545,000	+1,241,000
Total	11,320,000	15,966,000	+4,646,000

INTRODUCTION

The Environmental Health Sciences Research and Training Grant Program was initiated in FY 1964, within the administrative structure of the Bureau of State Services (EH). With the reorganization of the Public Health Service and the establishment of the Division of Environmental Health Sciences, those grant-supported activities which conformed to the mission of the new Division were assigned to the National Institutes of Health. Accordingly, the $11,320,000, as shown above, was transferred from the FY 1967 budget for Environmental Sciences Research and Training Grants, Bureau of State Services, (EH), Public Health Service.

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).

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Regular projects	$4,516,000	$6,202,000	+$1,686,000
General research support		719,000	+719,000
Special programs	2,500,000	3,500,000	+1,000,000
Total research grants	7,016,000	10,421,000	+3,405,000

The Division of Environmental Health Sciences supports research and research training on the phenomena associated with the source, distribution, mode of entry, and effect of environmental agents on biological systems as related to the health of human beings. The overall objective is to produce the basic knowledge and methodology for assessing the actual and potential risks associated with exposure to adventitious environmental hazards, and to determine tolerances and threshold of hazard to biological systems as a base for control policies and control technology.

These funds support research activities within universities, research institutes, and other public or private nonprofit institutions. They play a key role in stimulating and expanding investigations needed to: (1) define the physical, biological, and chemical hazards of the environment; (2) determine the significance of these agents to the etiology of acute and chronic disease processes; (3) develop new or improved methodology for analysis and characterization of the biological effects of known and potentially hazardous agents; and, (4) conduct epidemiological studies to test ideas on the relationship of environmental factors to disease in man, particularly in the ranges of low-level exposure involving long-term and cumulative effects as end points.

Support is provided for research which ranges from smaller and circumscribed projects to broad and composite programs that integrate the research skills and efforts of investigators with diverse training. Grants also make possible the establishment of Centers which are university-based resources for both research and training and are embedded in the substance of graduate education. Their 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. Center 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.

PROGRAM PLANS IN 1967 AND 1968

The FY 1967 budget of $4,516,000 for research projects provides for the continuing support of 37 ongoing investigations and for the activation of approximately 33 new projects. The net increase of $1,686,000 for FY 1968 will be used as follows: $1,273,000 for increased costs of noncompeting continuations and support of 13 additional noncompeting continuations; $405,000 for 6 competing projects and 1 supplemental request. The $719,000 is for the program commitment to the General Research Support Program.

The research supported by these grants will continue to emphasize mechanisms of toxic action in mammalian systems, biologic characterization of environmental agents, and synergistic effects of multiple factors. Special interest will be given to problem areas of tobacco and health, pesticides, heavy metals and trace elements, mycotoxins and other natural toxins, synthetic organic compounds, and other agents of environmental media which represent actual or potential health hazards.

During 1967, funds available for Centers will allow for continued support of 6 ongoing programs and the establishment of 2 new programs. The net increase of $1,000,000 in FY 1968 will support an expanded operation of 4 ongoing programs and will permit the activation of 3 or 4 additional Centers.

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	37	$2,860,000	50	$4,133,000	+13	+$1,273,000
2. Competing projects	33	1,556,000	39	1,961,000	+6	+405,000
3. Supplementals	(4)	100,000	(5)	108,000	(+1)	+8,000
4. Subtotal	70	4,516,000	89	6,202,000	+19	+1,686,000
5. Research and training centers		2,500,000		3,500,000		+1,000,000
6. General research support				719,000		+719,000
7. Total research grants		7,016,000		10,421,000		+3,405,000

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	22	$2,289,000	41	$3,773,000	+19	+$1,484,000
2. Competing	24	1,765,000	22	1,522,000	−2	−243,000
3. Supplementals	(10)	250,000	(10)	250,000	0	0
4. Total training grants	46	4,304,000	63	5,545,000	+17	+1,241,000

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 training 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 allow for local identification and selection of candidates with research potential, as well as provide funds for payment of stipends.

PROGRAM PLANS IN 1967 AND 1968

The graduate research training program will continue to support the availability of high quality training opportunities in environmental health. Continued emphasis will be given to the fields of environmental toxicology, stress physiology, bioengineering, and ecology. Funds available in FY 1967 provided continuing support for 22 ongoing programs and for the start of approximately 24 new graduate programs of research training. The $5,545,000 requested in FY 1968 will allow for continuing support of 41 ongoing programs, the renewal of 5 programs whose current support is scheduled to terminate; the initiation of 17 new programs (estimated) and provide for 10 supplements for expansion of ongoing graduate program of training. It is estimated that the budget will provide stipends to some 550 trainees.

Laboratory and clinical research

	1967 estimate		1968 estimate		Increase of decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	30	$193,000	148	$1,428,000	+118	+$1,235,000
Other expenses		1,313,000		2,647,000		+1,334,000
Total	30	1,506,000	148	4,075,000	+118	+2,569,000

INTRODUCTION

This activity supports the inhouse research programs in environmental health sciences at the National Environmental Health Sciences Center in the Research Triangle Park, North Carolina.

The increasing number of agents being introduced into the environment both intentionally and adventitiously requires an assessment of real and potential hazards by bioassy techniques and the elucidation of basic mechanisms and principles of biological action since testing of all environmental agents is manifestly impossible.

There are no sciences that have a peculiar or unique relevance to environmental health. Most can contribute to the study of groups of compounds which impinge biological systems in concentrations and for durations that are determined by environmental factors and with little relationship to the likes and dislikes of individuals or small or large population segments. Most of these have high inherent biological activity and impinge upon biological target systems for very long periods of time, usually in low concentrations. These compounds are potential hazards to health; generally speaking they do not have demonstrated capability to produce immediately demonstrable disease under the circumstances usually encountered. The examples of acute intoxication by high concentrations of these substances do not constitute a frame of reference against which the effects of chronic exposure at low levels can be predicted. Consequently, there is a critical need for a science base upon which to develop control measures to limit these hazards to health.

PROGRAM PLANS IN 1967

The efforts in 1967 will involve the development of a cohesive framework within which the various scientific disciplines and categorical needs concerned with environmental health can operate in a collaborative and interrelated manner to facilitate the achievement of maximum information for use in limiting deleterious effects of evironmental hazards.

Consideration in the development of program will be given to the determination of the need for study of both existing and potential hazards. This can be accomplished by the utilization of clinical, epidemiological, and biometric data identifying individuals or groups with signs and symptoms of toxicity as well as population segments at unusual risk to environmental hazards. A second base for program is the review on a continuing basis of the chemical and physical structure and properties of existing and potental environmental agents for the purpose of identifying those of likely toxicologic significance, e.g., compounds chemically related to known economic poisons, etc. The identification and determination of the extent of the hazard will be pursued along three lines of investigation: (a) the population involved, its size, characteristics, including geography, and occupation factors and sub-segments, such as extremes of age and associated diseases; (b) the nature of the agent, including its chemical, biological and physical properties which serve as indices of suspicion, and (c) the envronmental location—air, food and water.

The program for FY 1967 will involve the development and arrangement of facilities for the start of an animal colony and the availability of wet laboratory space for biochemistry, toxicology, experimental pathology and biology, as well as office space for the initiation of epidemiology and biometry studies.

PROGRAM PLANS IN 1968

The projected increment of 118 positions and $2,569,000 in Fiscal Year 1968 will provide for additional staffing and completion of the nucleus for the permanent animal colony, as well as initiation of the first phases of research in basic and applied disciplines. The component units of the Center will have disciplinary or categorical identification to facilitate recruiting of scientific staff. However, the basic concern of the Center will be clearly related to problems in environmental health. The task force type of operation will characterize its basic approach to problem solving. This problem-solving, operational base of the Center will extend from studies at the molecular level to those involving the response of the intact host. Quantitative biological techniques of the most advanced and elegant nature will be used for studies in depth.

A major pressing need is the establishment of criteria which can accurately and reliably identify animal and other experimental systems having the highest

possible level of predictability in assessing potential as well as existing environmental health hazards. Accepting that compatibility of findings in man an experimental species represents the most meaningful base for extrapolation, the preeminent role of bioassay in all planned studies becomes apparent. To further assure relevance of bioassay procedures to man, circumstances of human exposure will be duplicated to the maximum extent possible using the most modern and elegant of exposure techniques and manipulation of environmental conditions, including total body exposure under controlled conditions. Exposure concentrations approximating those occurring ambiently will be used. Certain protocols will require the induction of graded injury to experimental species so as to study the effect of reduced reserve and other less than optimal states on the response to environmental agents. It is to be recalled that a significant segment of the population is below optimal physiologic equilibrium because of extremes of age or the presence of antecedent or concomitant disease.

The usefulness of certain environmental agents of undetermined or potential hazard requires that diligent effort be directed to determining the validity of the no threshold concept for certain classes of compounds alone and in combination with physical agents.

There is growing recognition and corallary concern over the ability of the intact host to store certain environmental agents in various tissues and organ systems. These stored agents may exert a depot effect and may result in a progressive increase in the response of the individual to enviromental agents. There remains, in addition, the need to define the reasonableness of "threshold" or "no threshold" concepts and the assessment of the effects of combinations of contaminants working in concert in an additive, potentiating or neutralizing fashion.

Fundamental studies are planned to investigate the concept of "total body burden" as a factor inducing biological change as opposed to the influence of differing amounts of individual environmental contaminants accepted by the body over differing periods of time.

An inquiry into factors that determine varying degrees of host susceptibility to different forms of intoxication is planned. The possible modifying role of enzymatic, immunologic and genetic factors will be investigated. This approach should also provide leads for purposefully altering host-environment relationships with enhancement of resistance of individuals in unavoidable high risk environment through preservation and/or potentiation of defense mechanisms.

The quantification of hazard, and the mechanisms of environmental action will require the conduct of a research program embracing laboratory sciences in the areas of pharmacology, toxicology, chemistry, biology and pathology. These disciplines will be directed to an understanding of the fundamental basis and the cellular and sub-cellular mechanisms of acute toxicity, chronic toxicity, carcinogenesis and mutagenesis as the result of physical and chemical agents. With the already exponential increase in knowledge at the cell and organelle level, optimism appears warranted for the development of generalizations and principles on which to plan program and predicate action. It is recognized that the identification of toxic agents in the environment need not inevitably connote an adverse biological effect. Such criteria are critically important and the study of effects at the cellular level is imperative.

The chemical basis (kinetics of organic reactions under conditions of high dilution) for the generation and introduction of chemical intoxicants within the environment itself is in need of elucidation. These studies are not intended to relieve industry of its responsibility for environmental controls or product safety, but rather to provide for investigations to establish a scientific basis for protection of the public. Present techniques for micro-quantitation have achieved sensitivities that could only be remotely anticipated as recently as a decade ago.

Complementing the laboratory studies of some and as the point of origin of others will be a broad program of demography which will be accomplished through the application of epidemiological and statistical techniques. These studies will include descriptive, as well as analytical epidemiology, the former concerned with the assembly of data on variation in risk to environmentally determined or caused morbid states utilizing a broad spectrum of demographic variables (occupation, residence, age, sex, race, antecedent and concurrent

disease, etc., etc.) Analytical epidemiology is concerned with the development of individually tailored protocols designed for the purpose of testing hypothesis 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 the end points rather than the more obvious acute responses. The latter will certainly also be of important concern. Critical in the implementation of research in this area will be the identification and esablishment of human population laboratories on a geographic, occupational, and other environmental bases.

Review and approval of grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	14	$176,000	18	$181,000	+4	+$5,000
Other expenses	--------	125,000	--------	175,000	--------	+50,000
Total	16	301,000	18	356,000	+2	+55,000

INTRODUCTION

Under the Associate Director for Extramural Research, this activity supports the scientific and administrative staff responsible for the review, negotiation, processing and awarding of all grants. The staff obtains complete information about all grant applications and, in cooperation with study groups, makes recommendations for the consideration of the council which recommends approval or disapproval of applications.

The scientific staff makes project site visits to grantee institutions to evaluate grant programs, survey manpower needs, determine with the administrative staff type and level of support, need for expansion of facilities, etc. Administrative and operational staff conduct financial reviews and arrange for liaison with their counterparts in the business offices of grantee institutions.

The increase of $55,000 includes $28,000 to provide for two new clerical positions and supporting services. The remaining $27,000 is an increase over 1967 for the centrally furnished services from the NIH Management Fund.

Program direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	10	$108,000	10	$123,000	0	+$15,000
Other expenses	--------	87,000	--------	95,000	0	+8,000
Total	10	195,000	10	218,000	--------	+23,000

INTRODUCTION

This activity supports the Director of the Division and scientific and administrative staff who assists in the planning, supervision and technical direction of the program.

The increase of $23,000 includes $15,000 for the annualization of positions new in 1967. The remaining $8,000 provides for additional supplies and materials and an increase of $6,000 for centrally furnished services for the NIH Management Fund.

New positions requested, fiscal year 1968

	Grade	Annual salary
Research:		
Associate Scientific Director (1)	GS-17	$22,760
Medical officer (2)	GS-16	40,150
Executive officer (1)	GS-16	20,075
Medical officer (2)	GS-15	36,314
Scientist (4)	GS-15	70,200
Statistician (1)	GS-15	17,550
Administrative officer (1)	GS-14	15,106
Medical officer (5)	GS-14	85,990
Engineer (1)	GS-14	15,106
Scientist (8)	GS-14	120,848
Mathematician (2)	GS-14	30,212
Statistician (1)	GS-14	15,106
Scientist (7)	GS-13	90,111
Administrative officer (1)	GS-13	12,873
Medical staff assistant (2)	GS-13	25,746
Statistician (1)	GS-13	12,873
Scientist (8)	GS-12	87,416
Statistician (1)	GS-12	10,927
Administrative officer (1)	GS-11	9,221
Scientist (12)	GS-11	110,652
Statistician (1)	GS-11	9,536
Research technologist (6)	GS-9	46,176
Medical staff assistant(1)	GS-9	7,696
Administrative assistant (1)	GS-9	7,696
Research technologist (10)	GS-7	64,510
Statistical assistant (1)	GS-7	6,451
Laboratory assistant (8)	GS-5	42,648
Clerical assistant (5)	GS-5	26,655
Laboratory assistant (5)	GS-4	23,880
Animal caretaker (4)	GS-3	17,076
Laboratory assistant (5)	GS-3	21,345
Animal caretaker (7)	GS-2	27,475
Laboratory assistant (2)	GS-2	7,850
Total (118)		1,158,230
Review and approval of grants:		
Clerical assistant (1)	GS-4	4,776
Clerical assistance (1)	GS-3	4,269
Total (2)		9,045
Total new positions, all activities (120)		1,167,275

THURSDAY, APRIL 13, 1967.

GENERAL RESEARCH AND SERVICES, GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES, AND GENERAL RESEARCH SUPPORT GRANTS

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, CHIEF, OFFICE OF INTERNATIONAL RESEARCH
DR. ARNOLD W. PRATT, DIRECTOR, DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
POSEY B. HOWELL, JR., EXECUTIVE OFFICER, DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

GENERAL RESEARCH AND SERVICES

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	1,999	2,938	3,346
11.3	Positions other than permanent	52	176	193
11.5	Other personnel compensation	9	11	12
	Total personnel compensation	2,060	3,125	3,551
12.0	Personnel benefits	226	356	399
21.0	Travel and transportation of persons	324	766	792
22.0	Transportation of things	51	81	83
23.0	Rent, communications, and utilities	252	231	287
24.0	Printing and reproduction	3	71	74
25.1	Other services	999	3,160	3,441
	Project contracts	1,288	1,603	1,816
25.3	Payment to "National Institutes of Health management fund"	642	742	818
26.0	Supplies and materials	58	98	123
31.0	Equipment	839	1,292	1,495
41.0	Grants, subsidies, and contributions	51,720	60,175	68,262
99.0	Total obligations	58,461	71,700	81,141

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	308	329	349
Full-time equivalent of other positions	9	16	16
Average number of all employees	215	291	338
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Division of Research Facilities and Resources:			
(a) Grants:			
(1) Research	47,645	51,718	57,198
(2) Fellowships		100	200
(3) Training		250	318
(b) Direct operations:			
(1) Collaborative research and development	2,785	1,766	1,991
(2) Review and approval of grants	1,232	1,395	1,511
(3) Program direction	645	740	796
2. Office of International Research:			
(a) Grants:			
(1) Research	2,877	6,907	9,166
(2) Fellowships	1,198	1,200	1,380
(b) Direct operations:			
(1) International research	1,240	3,326	3,372
(2) Training activities	165	183	187
3. Division of Computer Research and Technology: Direct operations	1,315	3,767	4,675
4. Engineering development		348	347
Total program costs, funded [1]	59,102	71,700	81,141
Change in selected resources [2]	−641		
10 Total obligations	58,461	71,700	81,141
Financing:			
16 Comparative transfer to from (−) other accounts	100	−3,447	
25 Unobligated balance lapsing	1,906	268	
New obligational authority	60,467	68,521	81,141
New obligational authority:			
40 Appropriation	60,469	68,534	81,141
41 Transferred to—			
"Office of the Surgeon General, Salaries and expenses (42 U.S.C. 226)	−2		
"Operating expenses, Public Buildings Service," General Services Administration (80 Stat. 674)		−13	
43 Appropriation (adjusted)	60,467	68,521	81,141
Relation of obligations to expenditures:			
10 Total obligations	58,461	71,700	81,141
70 Receipts and other offsets (items 11–17)	100	−3,447	
71 Obligations affecting expenditures	58,561	68,253	81,141
72 Obligated balance, start of year	113,592	46,414	48,940
74 Obligated balance, end of year	−46,414	−48,940	−61,369
77 Adjustments in expired accounts	−5,896		
90 Expenditures	119,843	65,727	68,712

[1] Includes capital outlay as follows: 1966, $242,000; 1967, $1,292,000; 1968, $1,495,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1965, $3,072,000 (1966 adjustment, −$1,000); 1966, $2,431,000; 1967, $2,431,000; 1968, $2,431,000.

Grants for Construction of Health Research Facilities

Program and financing

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Program by activities:			
	Grants:			
	1. Health research facilities	50,032	35,001	50,000
	2. Centers for research on mental retardation	6,234	6,026	
10	Total program costs, funded—obligations (object class 41.0)	56,266	41,027	50,000
	Financing:			
21	Unobligated balance available, start of year	−293	−27	−15,000
24	Unobligated balance available, end of year	27	15,000	
40	New obligational authority (appropriation)	56,000	56,000	35,000
	Relation of obligations to expenditures:			
71	Total obligations (affecting expenditures)	56,266	41,027	50,000
72	Obligated balance, start of year	118,079	148,390	151,452
74	Obligated balance, end of year	−148,390	−151,452	−163,109
90	Expenditures	25,955	37,965	38,343

General Research Support Grants

Program and financing

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Program by activities:			
	1. Grants:			
	(a) General research support	39,200	41,700	43,200
	(b) Biomedical sciences support	5,000	6,000	7,500
	(c) Health sciences advancement support	1,000	4,000	11,000
10	Total program costs, funded—obligations (object class 41.0)	45,200	51,700	61,700
	Financing:			
11	Receipts and reimbursements from: Administrative budget accounts	−45,200	−51,700	−61,700
	New obligational authority			
	Relation of obligations to expenditures:			
10	Total obligations	45,200	51,700	61,700
70	Receipts and other offsets (items 11-17)	−45,200	−51,700	−61,700
71	Obligations affecting expenditures			
72.98	Obligated balance, start of year	35,845	39,096	39,096
74.98	Obligated balance, end of year	−39,096	−39,096	−39,096
77	Adjustments in expired accounts	−225	−11	
81	Balance not available, start of year		11	
82	Balance not available, end of year	−11		
90	Expenditures	−3,487		

Mr. NATCHER. The committee will come to order. At this time, Dr. Shannon, if you will, please, we would like for you to discuss with the committee matters pertaining to general research and services, grants for construction of health research facilities, and general research support grants. You have with you certain members of your staff that you will refer to from time to time with these items. We will be pleased to hear from you now.

GENERAL STATEMENT

Dr. SHANNON. Thank you very much, sir. Mr. Natcher, may I identify the specific people related to the specific activities? On my left is Dr. Heinz Specht, who is Chief of the Office of International Research. Dr. Arnold Pratt is Director of the Division of Computer Research and Technology right here. Dr. Thomas Kennedy is Director of our Division of Research Facilities and Resources.

AUTHORIZATION AND ORGANIZATION OF GENERAL RESEARCH AND SERVICES

I thought that I might introduce this rather complex series of very important activities. The activities of NIH which we have presented up to this time, while quite diverse, have one thing in common: each activity is conducted under a single legislative authority. The budget breakout for each is a simple reflection of how each authority will be used in program terms.

We now come to a series of very important activities, the routine budget presentation of which tends to confuse rather than clarify the relationship between legislative authority, on the one hand, and the administrative means we have found effective in translating these authorities into program terms, on the other. The activities covered by the "General research and services" appropriation are conducted under the general legislative authority of the Public Health Service to pursue scientific activities in the development of new knowledge important to the resolution of disease problems and the maintenance of health. These activities themselves—some with small dollar support, others with rather large dollar support—have in common one general characteristic: they exist to underpin the activities of NIH that are supported by a series of independent though related categorical appropriations and that are concerned with disease categories. They provide general support to grantee institutions within which the bulk of the research programs we support are conducted. To put it another way, they provide resources to the scientific community at large without regard to categorical disease programs but resources which are essential for the effective development and execution of each of the categorical programs and resources which, as programs, can best be managed by a central organization.

These centrally managed programs are contained either in the general structure of my office, as is the case with the Office of International Research and with engineering development activities, or in independent divisions, as is the case with the Division of Computer Research and Technology and the Division of Research Facilities and Resources.

General support of research and research resources

[Amounts in thousands]

	1967		1968		Change	
	Positions	Amount	Positions	Amount	Positions	Amount
Office of International Research	81	$11,616	81	$14,105		+$2,489
Division of Computer Research and Technology	89	3,767	104	4,675	+15	+908
Engineering development	6	348	6	347		−1
Division of Research Facilities and Resources:						
Operating programs (General research and services appropriation)	153	55,969	158	62,014	+5	+6,045
General clinical research centers		28,463		30,443		+1,980
Special research resources		10,850		10,850		0
Animal resources		3,100		5,100		+2,000
Primate centers		9,000		10,500		+1,500
Training, contracts and administration		4,556		5,121		+565
General research support grants (funded from each of the National Institutes of Health and National Institute of Mental Health appropriations having regular research grants)		51,700		61,700		+10,000
General research support		41,700		43,200		+1,500
Biomedical sciences support		6,000		7,500		+1,500
Health sciences advancement awards		4,000		11,000		+7,000
Health research facilities construction (separate appropriation, no-year funds)		41,027		50,000		+8,972
General program		35,001		50,000		+14,998
Centers for research on mental retardation		6,026				−6,026

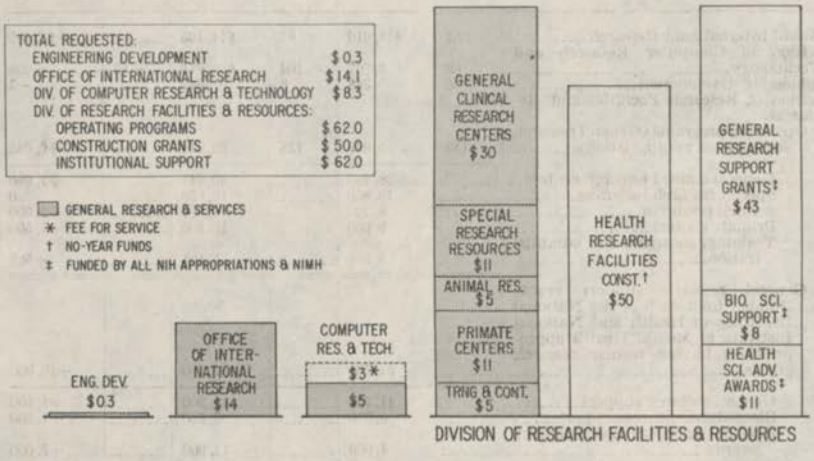
FUNDS FOR GENERAL RESEARCH AND SERVICES

The authorities were created by Congress, the administrative apparatus was created by NIH. The relationships between the two, Mr. Natcher, are presented in this chart and are summarized in the table that I believe Mr. Moyer has distributed to you. I believe it will clarify the written record of these proceedings if this chart can be reproduced together with an accompanying table, in black and white, in the record.

Mr. NATCHER. If there is no objection it will be inserted in the record at this point, Dr. Shannon.

(The document follows:)

FUNDS REQUESTED FOR GENERAL SUPPORT OF RESEARCH AND RESEARCH RESOURCES, FY 1968
(IN MILLIONS)



Dr. SHANNON. The summary of these activities is to be found in the congressional justification on page 340 insofar as these relate to general research and training activities. We have developed a chart that identifies the individual activities and identifies by color the different legislative authorities under which these are conducted. The activities shown in orange are authorized under our appropriation for general research and services. The activity outlined in yellow is authorized under our Health Research Facilities and Construction Act. The activities outlined in blue are authorized under our general research and training authority but the moneys for these activities are already contained, and have been justified, in the estimates for the individual categorical Institutes from which they are acquired on a percentage basis.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

The Division of Computer Research and Technology has been given divisional status because of its predicted growth in the immediate future and the predicted important role it will play in the biomedical sciences in years to come. We felt it highly advisable to establish an independent operating entity for this activity which has relevance to all of our programs across the board.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

Some years ago we created a Division of Research Facilities and Resources. It contains a series of resources programs including animal resources to supplement some of the recent animal legislation that was in the offing when this was set up some 3 or 4 years ago and now is in being as a result of the action of the last Congress. The resource centers, which we find convenient to centralize in this appropriation, include computer activities in universities, large biomedical laboratories

contained in one institution to service many institutions, and a number of small activities, which Dr. Kennedy will point out, that relate to training. The health research facilities construction is a separate appropriation. The Division also manages the general research grant program. These activities are noncategorical in nature. These expenditures are totally in the extramural area in support of the general research plant of the Nation. They will be discussed as three related activities by Dr. Kennedy.

I will limit the remainder of my remarks to two areas, questions that relate to the Office of International Research and those that relate to——

Mr. LAIRD. May I ask a question?

Mr. NATCHER. Yes.

EXPENDITURES FOR HEALTH RESEARCH FACILITIES CONSTRUCTION

Mr. LAIRD. Are we getting away from the chart now?

Dr. SHANNON. No. We will leave that chart as a backdrop for each of the items. But I would be glad to answer any questions at this time.

Mr. LAIRD. I do not understand the yellow block in that chart. We are going to spend more than $50 million on health research facilities construction? Is that an appropriation level or an expenditure level?

Dr. SHANNON. This is an expenditure level. The obligational authority for this activity is limited to $35 million this year.

Mr. LAIRD. So this is an expenditure level?

Dr. SHANNON. Yes, sir.

These grants will be obligated in the year 1968. You may recall, Mr. Laird, that this was a 3-year authorization. We went into the first year of this 3-year cycle during last fiscal year. This committee raised research facilities construction from $15 million to $50 million. As part of the reduction in expenditures this year, during fiscal 1967, we were asked to take $15 million that was available in 1967——

Mr. LAIRD. I understand that. You are using obligational authority that was granted in 1967?

Dr. SHANNON. $15 million of this was granted in 1967, $35 million is new obligational authority in 1968. The total obligational authority, as you recall, is $280 million over a 3-year period.

OFFICE OF INTERNATIONAL RESEARCH

Mr. Natcher, I would like to talk to the Office of International Research. There is an opening statement that I would like to file for the record, if I may.

Mr. NATCHER. It will be inserted at this point, without objection, Dr. Shannon.

(The statement referred to follows:)

STATEMENT BY DIRECTOR, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, ON INTERNATIONAL RESEARCH

Mr. Chairman and members of the committee, the Office of International Research is the focal point in the Office of the Director, NIH, for the administration of the international activities of the National Institutes of Health. It has responsibility for the policy formulation insofar as this is appropriate at the NIH level and the program analysis and coordination of the international activities of the

NIH. The office also acts as a point of liaison to the Science Office, Department of State, and The Office of Science and Technology of The President.

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 U.S.-Japan Cooperative Medical Science Program; the Special Foreign Currency Program, i.e., the P.L. 480 program, and the International Nutrition Program. The latter obtains the bulk of its support from funds contained within AID and DOD appropriations.

The Office of International Research has found it essential in the satisfaction of these responsibilities, and to maintain an awareness of the progress of science abroad, to maintain a small overseas staff. This staff is composed of seven professionals and eight supporting personnel. These are stationed within The Embassy organization of France for Western Europe, Brazil for Latin America and Japan for the Far East. Since their inception, these offices through their representatives have provided a continuous flow of formal and informal information to the Office of International Research. This has proved of valuable assistance to the Director of NIH and to the various Institutes and Divisions. The data collected have a growing function for programming unique research opportunities abroad.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

In response to the purpose of Section 2, Public Law 86-610, The International Health Research Act of 1960, "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, and research in training," the National Institutes of Health has since that time granted funds to five U.S. universities for the purpose of establishing International Centers for Medical Research and Training (ICMRT). The overriding consideration leading to this action program was the conviction that the research community within the U.S. was rapidly losing its competence to cope with problems of disease in any environment other than the sophisticated setting within the U.S. This had three factors:

1. Through lack of direct experience abroad, it was becoming increasingly difficult to appraise results of planned research derived from within the natural setting of a developing country and apply such results to the solution of domestic problems.
2. There was rapid loss of capability to take advantage of "natural experiments" that emerge as the result of rapid social change—again in developing countries.
3. In general, field studies could be undertaken for only short periods and lacked adequate laboratory backing.

To remedy these deficiencies and to create further opportunities of a stable nature, each Center is constituted as a separate department or institute within an American university, and investigations are conducted both in the United States and at an affiliated overseas site. Each ICMRT is staffed with American scientists for the conduct of research. The high calibre universities selected to participate in this program provide, for American scientists, unexcelled research and training opportunities in the requisite foreign setting. The natural proliferation of this international collaboratve research serves to assure a continuing attack upon widespread maladies of mankind.

The majority of research undertaken in an ICMRT embraces the spectrum of tropical medicine. The University of California in collaboration with the Institute for Medical Research, Kuala Lumpur, Malaysia, is conducting a study of infectious diseases transmitted from animals to man, including consideration of related socio-cultural factors.

At the Louisiana State University ICMRT in San Jose, Costa Rica, epidemiologic study of diarrheal disease, hookworm chemotherapy, and the natural history of amebiasis have been investigated. Emphasis at the Johns Hopkins University ICMRT in Calcutta, India, is directed toward work on the year-round distribution of respiratory and enteric viruses in pediatric populations. Studies are in progress on the distribution of hookworm, on portal hypertension in liver disease, and therapeutic trials in the attack upon smallpox. Special approaches to the basic disease processes in cholera and leprosy are also under way. In Lahore, West Pakistan, the University of Maryland ICMRT has set up comprehensive studies of insect-borne diseases, investigation of a tubercle-like bacterium

which causes lung disease, and work on the basic immunologic aspects of bacterial infection and disease. Nutritional studies have also been carried out using simple, inexpensive techniques for the mass screening of nutritional defects. Finally, at the Tulane University ICMRT in collaboration with the Universidad del Valle, Cali, Colombia, researchers have studied tetanus in newborn babies, ever present diarrheal diseases, Chagas Disease, various intestinal diseases caused by worms, malaria immunity, nutritional defects, and the epidemiology of suicide attempts. In addition, a number of viral diseases have been extensively studied at each ICMRT.

INTERNATIONAL POSTDOCTORAL FELLOWSHIPS

The International Postdoctoral Research Fellowship Program was initiated in 1958 to provide for an ability of advanced science settings in the U.S. to receive, as guests, a limited number of exceptionally-trained scientists from abroad. The presence of such vigorous and imaginative foreign Fellows of diverse origins in American laboratories has been demonstrated to be highly desirable because of the specific discoveries they have made, and also through the opportunity afforded their American colleagues at all levels of proficiency to learn of innovations, techniques and working concepts of some of the best young scientists developed in a foreign setting. Relationships between biomedical research institutions in the U.S. and in other countries are strengthened by active international sharing of knowledge, ideas and backgrounds. The training and experience acquired by the fellows themselves provides a stable base for scientific collaboration subsequent to the re-establishment of the young foreign scientist in his own scientific setting.

This program presently operates through the competition of candidates from 43 countries throughout the world. On the average in the last 4 years from an annual quota of 239 possible nominees only 175 were proposed due to the stringent criteria for consideration, and of these our program permitted the support of 104 of approximately 160 meritorious applicants. During the past 9 years, i.e. prior to 1967, 718 fellows have participated in this program involving 140 U.S. institutions. These scientists have not only taken the scientific fruits of their American experience to their home countries, but have also spread throughout the world the ideals and cultural assets gained here.

INTERNATIONAL RESEARCH CAREER DEVELOPMENT

Another program of this Office which assists in the training of internationally oriented United States biomedical scientists is the International Research Career Development Program. Through this program, ten Public Health Service Commissioned Officers are assigned for two years to research projects carried out overseas by PHS units or to projects of special interest to the Service carried out by other American organizations. Research experience and training of high quality can thus be assured, and at the same time fulfill an important need of the PHS by developing additional skilled manpower in support of American projects in foreign settings.

Research experience in overseas locations supported by the United States institutions enables an investigator to contribute directly to the ongoing research of the institution he is assigned to and in addition to broaden his own scientific capability, and attain greater understanding of the opportunities for scientific advances presented by disease abroad in an exotic setting.

INTERNATIONAL NUTRITION

An international multidisciplinary nutrition program, administered by the Nutrition Section of the Office of International Research, is financed by the Agency for International Development and the Advanced Research Projects Agency. The current program involves funding of $820,000 and $422,025 by those agencies, respectively. Its activities are directed at identifying nutritional problems, at understanding their basis, and at development of methods and techniques for their solution.

SPECIAL FOREIGN CURRENCY PROGRAM

The NIH portion of the Special Foreign Currency Program (PL 480), although governed by an appropriation to the Public Health Service, is administered by the Office of International Research. These funds are used by NIH to support collaborative medical research agreements of interest both to the

United States and to those countries where such currencies are available. At present there are about 150 active projects in seven countries, i.e., Burma, Egypt, India, Israel, Pakistan, Poland and Yugoslavia. These studies involve a broad range of fields including anemia, malnutrition, oral cancer, gastric cancer, brain tumors, hypertension and heart disease. This program is justified elsewhere in the Public Health Service budget.

UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM

The U.S.-Japan Cooperative Medical Science Program was initiated in fiscal 1967 under the authority of a Presidential Delegation of Section 5 of Public Law 86-610, The International Health Research Act. It is concerned with the diseases of mutual importance to health in the United States and in Asian countries. These diseases or categories of diseases include: cholera, tuberculosis, leprosy, viruses, parasitism, and malnutrition, and special preliminary review panels have been established to review projects proposed under each of these diseases or categories of diseases. This program will exert its emphasis through programmed research in the several areas of: Pakistan, India, Ceylon, Thailand, Indonesia, Philippines, Republic of Korea, Republic of China, Vietnam and Maylasia. Field research may be undertaken when deemed necessary or desirable. Projects of U.S. scientists will be supported by the United States and those of the Japanese scientists by Japan. Interest in this Program has been widespread and a number of grants and contracts, which meet the Program goals, have been approved for awards. As of a very recent date the list of awards covered 49 grants and 10 contracts. Details relating to these argreements can be made available if you would care to review them. The Office of International Research is responsible for the overall coordination and management of the U.S.-Japan Cooperative Medical Science Program. In addition, however, the appropriate NIH categorical Institute scientific staff and the Advisory Councils will review and approve the project applications, and the Institute staff will assist in their administration. If the Committee wishes we can provide a recent report on this program which was submitted to the President.

The request of the Office of International Research is $14,105,000 of which $7 million is for U.S. activities contained in the U.S.-Japan Cooperative Medical Science Program.

Dr. SHANNON. I would like to discuss this activity, in part, in the light of some of the questions that arose with respect to international activities during the hearings. Some of my comments I think will clarify some of these situations.

The functions of the Office of International Research are six.

Mr. NATCHER. In order that the members may understand, this comes under general research and services?

Dr. SHANNON. Yes, sir.

Mr. NATCHER. Very well. Go right ahead.

Dr. SHANNON. As represented by this block covering, in the aggregate, $14 million. Now, as I said, the functions are six.

POLICY FORMULATION

One function is policy formulation covering the relationship of NIH to world science in general. This function is performed by the staff in Bethesda, supplemented by small staffs in each of four foreign cities: Paris, Rio de Janeiro, Tokyo, and New Delhi. Foreign staff activities are the responsibility of seven profesionals assigned to the U.S. embassies in these cities solely to satisfy our own requirements. This activity amounts to $938,000 for personal services and $434,000 for other objects.

INTERNATIONAL FELLOWSHIP PROGRAM

The second function relates to the conduct of a small international fellowship program which brings to this country about 100 research fellows each year. These are selected primarily on the basis of their individual excellence but with a view to the contribution the fellow can make to the enrichment of the university which serves as his host. The fellows are appointed initially for 1 year; in selected cases they are invited to stay on an additional year if this would appear to be desirable. These fellows bring unique skills to U.S. laboratories and have served as an important bridge for the later development of collaborative activities between our institutions and the institutions in the country of origin of the fellow.

This program amounts to an expenditure of $1,967,000 of which $1,380,000 is for stipends and $587,000 is made available in grants in order to set these fellows up in the initial stages of their return home and provide a base for collaborative activities.

INTERNATIONAL CENTERS FOR RESEARCH AND TRAINING

The third function supported by this appropriation is the maintenance of five international centers for research and training. One of these is run by Johns Hopkins University and is in Calcutta, India; the second by the University of California in Kuala Lumpur, Malaysia; the third by the University of Maryland in Lahore, Pakistan; the fourth by Tulane University in Cali, Colombia, and the fifth by Louisiana State University in San Jose, Costa Rica. This activity is funded for a wholly selfish purpose. While it does, no doubt, benefit the host country, the purpose is to provide to the American scientists, both young and well established, an opportunity to work on problems of general consequence to the United States but in places that provide excellent opportunities for the observations and study of diseases in settings not available in this country. The program also provides, as an essential for a stable field operation, support of the home-based university operation. In this way it is possible to obtain broad involvement of the home university in the overseas activities.

This activity is supplemented by a small, direct-training program which includes the support of 10 American scientists at a projected rate of $187,000 a year. While we have found this an effective device for training U.S. citizens in exotic environments, where unique experimental opportunities exist, we propose to terminate the program when the current assignment of the professionals is completed, that is, at the end of fiscal 1969. We are convinced that the mechanism developed is clumsy and that the same results can be obtained by simpler means. The activity covering the international centers operates at a level of $2.8 million and is not proposed for any increase.

USE OF PUBLIC LAW 480 FUNDS

The fourth function involves staff support for the effective use of such funds as are available to support research abroad through the use of Public Law 480 funds. In this program we will expend during 1967 $4.3 million and during 1968 $4.1 million. This estimate will be

presented for your consideration as part of a consolidated Public Law 480 program by the Public Health Service.

The effective utilization of these U.S.-owned currencies in the furtherance of our general objectives requires a central focus for staff support. This is contained in our Office of International Research. The activities supported are an extension of the scientific activities of our various Institutes. With this central staff, there is no need to have staff services in each of the Institutes that make use of this support device. Such centralization makes for a highly efficient type of program execution.

JAPANESE-AMERICAN COOPERATIVE PROGRAM

The fifth function is the staff direction for the United States of the programs developed under the agreement reached between President Johnson and Premier Sato for the development of a collaborative program involving American and Japanese scientists intimately concerned with a number of common but limited objectives. The areas of work selected for inclusion in this program are of concern to the United States domestically, to Japan domestically and, in addition, to Southeast Asia, generally.

The program objectives are the development of an immunological means to prevent tuberculosis, the related problem of a better understanding of the disease mechanisms of leprosy, and probings into the isolation and growth of the causative agents and into the management of the disease by therapeutic agents.

Secondly, a study of problems relating to disease caused by insect-borne viruses. Included in these studies which parallel some of our own studies in Panama and in this country are the various encephalitic diseases and the hemorrhagic disorders which Dr. Davis discussed with you at some length yesterday.

The third group of studies inquires into the consequences to human development of nutritional deficiencies and in association with the Department of Agriculture studies have been conducted aimed at the development of cereal grains with a higher protein content and higher quality protein.

Fourth, there are the studies aimed at development of solid immunizing agents for cholera which we discussed at some length in relation to the Allergy Institute.

And, finally, the study of two parasitic diseases, filariasis and schistosomiasis.

The expenditures for these programs are of two types. The bulk of the expenditures are from funds for the normal programs of the Institutes developed wholly for purposes of solving domestic problems. A smaller amount will be devoted to problems of interest to American scientists but of more urgent concern to population groups of southeast Asia. The aggregate expenditure of all directly relevant programs in this activity will be at approximately $7.1 million in fiscal 1968 of which $2 million will be for contracts and $5.1 million for research grants.

I might emphasive that the bulk of these funds will be expended in support of American scientists, or in extension of their work, and will not be used to support the Japanese part of the collaborative program. There is little of this activity that is not of direct consequence

to the American people in a domestic sense. There is nothing contained within this program that is not of direct consequence to our Armed Forces, and to our citizens who travel or work abroad. The program though falling within the general authorities of NIH and its operational institutes and divisions, is specifically conducted under the Presidential authorities contained in Public Law 86–610 and delegated to NIH for these purposes. I would point out that these programs have no relations to an AID-type activity.

The final program of the Office of International Research is the conduct of research in nutrition. This activity is primarily conducted by OIR using NIH as a general focus. It is performed to satisfy some of the needs of the Department of Defense and AID for scientific information. The research is supported by funds transferred from ARPA of DOD and from AID. It consists of nutritional surveys of civil populations leading to recommendations of how deficiences can be most effectively countered. It also contains research projects that stem more or less directly from such survey activities. This activity is financed by the transfer from ARPA of some $820,000 and the transfer from AID of some $422,025. In the aggregate, the expenditures amount to $1,242,025.

I think, Mr. Natcher, that makes fairly explicit the individual programs that are contained in the Office of International Research.

We would be glad to discuss these activities or turn immediately to the second item.

Mr. NATCHER. All right. You may proceed in the order you desire.

ENGINEERING DEVELOPMENT

Dr. SHANNON. There is an activity that I have overlooked. It is the very thin sliver of program that is called engineering development. It amounts to $350,000.

Mr. NATCHER. What does this consist of, Dr. Shannon?

Dr. SHANNON. This, at the present time, is a sum of money that was made available, specifically at the recommendation of this committee, to develop a new organizational structure and a more adequate method of handling, within a consolidated operation, the technical elements of NIH that are engaged in bioengineering and engineering development, to furnish leadership and competence for the further evaluation and growth of engineering development, particularly insofar as the utilization of industry is concerned and to provide for critical surveillance and review of all NIH contract activities in this field. We have made proposals to the Secretary which look toward the establishment of such a central organization. The $350,000 in the 1968 budget will permit the development of the central organization, the continuation of the planning for this operation and the beginning of operations at a modest level in 1968.

Mr. NATCHER. All right. Thank you, Dr. Shannon.

Dr. SHANNON. This is Dr. Arnold Pratt, Director of the Division of Computer Research and Technology.

Mr. NATCHER. Dr. Pratt, we will be pleased to hear from you at this time. As I understand now, Dr. Shannon, this also comes under "General research and services" as set forth on your chart.

Dr. SHANNON. Yes, sir.

Division of Computer Research and Technology

Dr. Pratt. The general utility of computers is well recognized. Indeed the 1966 hearings before the Subcommittee on Census and Statistics of the Committee on Post Office and Civil Service of the House of Representatives present eloquent testimony to the value of the digital computer.

The digital computer can manipulate vast quantities of data rapidly and accurately. The machine epitomizes the new methodology of computation which can be applied in the solution of problems in every discipline. The effectiveness of this new methodology lies in providing cheaper, faster, or better solutions to specific problems and in providing the capability of undertaking new problems which, heretofore, were too large to compute by human or electromechanical means.

Recognition of the potential value of computation and the need for an integrated computer science program led to the establishment of the Division of Computer Research and Technology in 1964. The mission of the Division is threefold:

First, the Division conducts research and development in mathematics, statistics, computer programing, and computer systems engineering aimed toward the more effective use of computers in biomedical research.

Second, the Division collaborates with the NIH administration, program representatives, and individual scientists on a wide range of projects that lend themselves to computing.

Third, the Division provides centralized computation and data processing service for all of NIH. This latter activity is self-supporting on a fee-for-service basis administered through the NIH service and supply fund. The funds being requested here today will be used to support the research and development programs of the Division.

I might turn back to Dr. Shannon's chart, if I may. I point out that there is an added block within our dollar allocation of something in excess of $3 million. These dollars are earned by providing service to the Institutes and the programs which you have heard during the past few days.

If I may, I would like to take the opportunity to review in a historical sense what has happened to the computer in biomedical science because in many ways it is interesting.

HISTORICAL REVIEW

The explosive growth of data processing at NIH had its beginning prior to 1958, when all data processing was done on a battery of electrical accounting machines. This equipment had a minimum of arithmetic capability and served only for tabulation. Irrespective of this deficiency, several excellent epidemiological studies were done, among them a pioneer study which correlated lung disease with tobacco smoking as a function of such variables as age, sex, type, duration, and amount of smoking.

In mid-1958, a computer of modest power was acquired. The epidemiological and administrative problems were rapidly transferred to the new machine. The biomedical scientists began to use the computer for rapid, accurate evaluation of experimental data.

Beginning in late 1959, computer utilization grew very rapidly and computer capacity grew correspondingly.

I will not recite how we have changed the machines, and so forth, except to acknowledge at this time we are again in the midst of one of those difficult changes to new equipment of greater capacity and broader flexibility so that we may indeed meet the unique means of other research programs.

Currently, transition to a newer generation of computing equipment is being made to serve the expanding needs at NIH.

The experience of NIH has been in many ways typical of the national scene. Prior to 1959–60, the promise of computer technology for biomedical science was accepted by only a few investigators. The majority of scientific leaders viewed the new technology with reservations and even skepticism. This was not an irrational attitude, really. Computers had been designed and developed by engineers working closely with mathematicians and logicians who used the computer for solving well-formulated mathematical and statistical problems. Computers and computer programing languages appeared to be ill suited for the relatively imprecise date obtained from biological systems. Also, the supply of mathematical consultation and computer equipment to the biomedical scientist was severely limited. Fortunately, the forward-looking programs of the Federal Government through a number of agencies but, more importantly, through NIH, made public funds available for advanced training of personnel and the acquisition of computing equipment for biomedical scientists. A rapid growth in the biomedical application of computers resulted.

Thus, in the space of a few years, biomedical computation and automatic data procesisng have become a significant part of the biomedical research and engineering effort. There have been no spectacular breakthroughs directly attributable to the computer. The availability of the computer has, however, accelerated the orderly evolution of biomedical science.

Dr. Shannon, in an opening statement earlier, noted that biomedical science was still something of a largely empirical thing; the basic laws by which we may gain great understanding were not well formulated. The computer is playing an important role here. The explicit nature of computer programing has forced the physician and scientist to acquire data with greater precision and store these data in an easily retrievable form. The investigator now performs quantitative statistical evaluations routinely on his data. Impressionistic and descriptive science is giving way to more quantitative science which routinely uses mathematical and statistical tools.

COMPUTER APPLICATIONS AT NIH

Today the NIH staff use the computer for a multitude of tasks in the conduct and management of NIH research programs. These tasks comprise four general data processing areas.

The NIH administration utilizes the computer in the management of procurement and plant maintenance operations, the control of numerous property inventories, the performance of several fiscal and accounting tasks, the maintenance of personnel files, and so forth.

The $800 million extramural awards program represents a very large computer-based information storage and retrieval system. This program, which is coordinated by the Division of Research Grants, comprises a highly varied set of data processing tasks dealing with receipts, review, and dollar commitment activities within the Institutes and Divisions at NIH.

Epidemiological and biometrical problems, the attempts to find and define disease in a population, of course, exist in every Institute at NIH, reflecting the concern of the research medical community for all aspects of disease in the human population. A few examples of this type of computer application may be helpful: the National Heart Institute is conducting a large, long-term study to determine the time-related physiological changes associated with heart disease; the Perinatal Study of the National Institute of Neurological Diseases and Blindness focuses broadly on the incidence and contributing causes of birth injury and mental retardation; the National Cancer Institute maintains a huge registry of reported cancer in human subjects. This registry is used in the continuing evaluation of therapy—surgery, radiation, drugs, and hormones. Studies of this kind were virtually impossible prior to the advent of data processing because of the sheer volume of data involved.

A significant portion of the computer workload relates to laboratory and clinical research problems. The bulk of this work involves the evaluation of experimental data using traditional statistical concepts and mathematical procedures. These procedures were heretofore done on desk calculating machines, and so forth, and the size of the chore simply limited what one can do.

Aided by the computer, the scientists are making increased use of complex mathematics to describe biological systems. This is an important aspect really.

For example, mathematical approximations have been made which relate electrical activity and the associated movement of sodium and potassium ions across nerve cell membranes. Computer programs exist which allow the quantitative description of the stepwise metabolism of radioactively labeled metabolites such as glucose or fatty acids or the mineral elements such as iron. The hydrodynamic properties of airflow in the lungs and bloodflow in the heart and great vessels have been subjected to quantitative description. These mathematical descriptions represent models of the biological system under study and they become very powerful supplements to the continuing laboratory or clinical investigation. Using these models it is possible to define precisely the needs for future experiments.

To satisfy the requirements of the NIH research programs, insofar as computation is concerned, the Division maintains a strong central computing facility, including advanced computer programing services.

Since April 1966 the Division has devoted a significant portion of its resources to adapting the new computers to meet the unique needs of NIH.

In addition, the Division maintains a mathematical and statistical consulting resource. The research and development program of the Division in support of the NIH research programs involves the development of new and improved computing techniques and the development of new mathematical and statistical procedures. So I think you can see why we need the mathematical and statistical resource.

Our present research program emphasizes the development of more powerful mathematical procedures for use in the clinic, particularly in the area of cardiac function following surgical repair of malformations.

The first of a series of new computer programing languages has been completed. These new languages enable the scientist to utilize the computer independent of skilled programing personnel.

The computing capability of the central facility is being extended into the laboratories and the clinics by the development of a teleprocessing capability. Given remote access to the computer, scientists will be able to evaluate data and use mathematical modeling methods on a timely basis at the site of the ongoing investigation.

Automatic processing of English language is an important need in science, education, and industry. Natural language is the systematic means by which ideas, concepts, descriptions, and feelings are communicated. The aim of automatic language processing is much more than just word matching in the computer. The larger need is to create computer programs which "understand" the meaning of a specific communication.

The Division is conducting studies in this research area. Significant success has been achieved in developing a computer-based system to process the English language diagnostic statements of the pathologists. The computer accepts and "understands" the written diagnostic statements and organizes the data automatically within the framework of pathology concepts incorporated in the computer program. This system now serves both clinicians and pathologists at NIH in conducting retrospective studies or in designing projective studies.

SUPPORT TO THE CLINICAL CENTER

The Division is also supplying staff assistance and financial support to the clinical center in the application of computers to patient care activities. Significant support is being given to the highly innovative research program directed toward automating a large number of the analytical procedures in the clinical pathology laboratories. Success of this program will have a large impact nationally on future patient care activities.

Because of the large costs involved, it has been agreed that a cautious approach must be taken in the creation of a computer-based information system for pharmacy functions, medical records, admissions and discharges, outpatient scheduling, dietetics, and so forth, in the clinical center. The Division staff is continuing in the systems analysis of this total complex problem searching for an economic solution to a pressing need.

In summary, the primary responsibility for designing, conducting and interpreting individual scientific investigations rests with the Institutes at NIH. In support of these investigations, the research and development programs of the Division are being organized to provide collaborative, consultative, and service support in all aspects of computer technology.

I have only been on this job a year, but I can say now, the imaginative research programs of the several Institutes present no end of challenging opportunities.

Performance of the Division's mission is restricted only by limiting resources, especially personnel; there is an acute shortage—a national shortage—of personnel skilled in computation. It is gratifying, however, to report the recruitment of mathematical and engineering leadership sufficient to have activated the Physical Sciences Laboratory and the Computer Systems Laboratory during this fiscal year.

To support the continuing research programs and expand developmental research efforts in systems development, pattern recognition, and computational linguistics, a budget of $4,675,000 is requested for 1968, representing an increase of $908,000 and 15 positions.

Mr. NATCHER. Dr. Pratt, we want to thank you for your statement and Dr. Shannon, as I understand now, we will hear from Dr. Thomas J. Kennedy, Jr., who will discuss with the committee the program under "Health research facilities construction."

Is that correct?

Dr. SHANNON. It is, but he also will discuss the residual portion of the "General research and services" and the blue elements that discuss general research and training authority. These are intimately related elements of this program.

Mr. NATCHER. Dr. Kennedy, we will be pleased to hear from you at this time.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

Dr. KENNEDY. I welcome this opportunity to appear before you in behalf of the programs of the NIH for whose immediate administration I am responsible—those of the Division of Research Facilities and Resources. The mission of this Division is to provide the Nation's scientific community with the solid foundation and basic complement of facilities and resources essential to progress in medical research. The programs presently operated by this organization can best be understood if placed in historical perspective. By the mid-1950's the NIH, with the enthusiastic and generous support of the Congress, had established a series of research and research training grant programs under the aegis of the several categorical Institutes. However, expansion of the attack on disease and death reached a limit at about that time, due to a severe deficit in the laboratory and clinical space necessary for the conduct of research. It was not until 1956, with the passage of the Hill-Bridges Health Research Facilities Act, that a systematic program emerged which enabled the NIH to join with non-Federal biomedical research institutions to construct and to equip, on a share-and-share-alike basis, facilities for health-related research.

The Hill-Bridges Act was the first important program in which the NIH focused on the needs of institutions, rather than on those of individual scientists. Over the next few years, however, the problems of institutions—the basic organizational units in which research is performed and research training conducted—emerged as major concerns of both the NIH and the Congress, and by 1962 the Congress had authorized and appropriated funds for a complex of programs designed to assist research institutions as such. In that year, these programs were administratively grouped in a new organization, the Division of Research Facilities and Resources, on the ground that they

comprised a natural unity, predicated on the concept that institutions, if they are to participate with the Federal Government in an attack upon health problems of broad public import, required support in their own right.

With this brief historical introduction I propose to review the specific program components of the Division, beginning with those elements included in the "General research and services" appropriation, moving on to the health research facilities program, and closing with a description of the general research support program.

GENERAL CLINICAL RESEARCH CENTERS

Clinical investigation—the study, in the human subject, of the cause, natural history, and treatment of disease—has been the springboard from which almost every major advance in medical science has been launched into the domain of medical practice. Perhaps even more importantly, clinical observation—the study of "nature's experiments" —has frequently provided clues which have stimulated extremely important and fruitful progress in the basic biomedical sciences. Like all modern science, the effective prosecution of clinical research demands an environment that provides the complex resources, facilities, and instrumental ensembles needed to collect precise and accurate information. Recognizing this fact, the Congress began in 1960 to provide funds to the NIH to inaugurate a program to establish general clinical research centers in appropriate institutions throughout the country.

Each general clinical research center is an independent research unit, most frequently located within a large hospital complex, and usually affiliated with a medical school. A typical center consists of 10 to 12 hospital beds, the staff necessary for operation, a dietetic kitchen, and various other supporting resources that enable clinical research to be performed under conditions of careful control and optimum patient care. Funds awarded in this program may be expended for the renovation of space to establish the center, and for equipment, hospitalization reimbursement, salaries of professional personnel, and other necessary operating expenses.

As of January 1, 1967, awards had been made to fund 91 centers in 74 institutions, encompassing 1,130 hospital beds, dedicated solely to research.

Although the general clinical research center program is less than 7 years old, it has already made many significant contributions to modern clinical medicine, some of which we have reported to this committee on previous occasions. The following are examples of research currently underway:

Kidney stones, the vast majority of which initially manifest themselves in otherwise healthy individuals, are not only disabling but they are likely, if untreated, to cause serious disease and, ultimately, complete destruction of the kidney. Thus, it is imperative to discover their cause and to learn to prevent them. Recent studies revealed a substance in normal urine that prevents the precipitation of calcium and phosphate—two principal components of most kidney stones. This substance, absent in patients who form stones, can be restored to the urine when phosphate salts are administered by mouth. Efforts to isolate and

characterize this "antistone" substance indicate that it is a single polypeptide and work is continuing to make further characterization possible. These studies will be of very great value in understanding the mechanisms of kidney-stone formation and in learning how to prevent it.

A new method for the detection of cancer of the cervix is under intensive study. The technique allows visual recognition of cancerous and precancerous tissues. This visualization is possible because such cells selectively and differentially accumulate a chemical compound, hematoporphyrin, which exhibits vivid fluorescence when exposed to ultraviolet light. In addition to its usefulness as a method for the detection of lesions, the technique may also be extremely helpful in assessing whether all of the cancerous tissue has been removed by treatment.

The by now well-launched general clinical research center program has provided many institutions with superb facilities for the careful study of the hospitalized patient. On the other hand, a major fraction of human disease occurs in ambulatory patients who presently escape the careful study they warrant. Currently, outpatient facilities in most institutions are grossly inadequate to permit the careful observations and the precise measurements necessary for the emergence of new scientific knowledge. To the degree that funds are available, the DRFR plans to inaugurate a program to establish institutional facilities and resources for the study of this extremely important domain of human disease, as recommended by the report of the Senate Appropriations Committee, submitted in connection with our appropriation for fiscal year 1967.

To provide continuing support for this most important general clinical research center program in fiscal year 1968, $30.4 million is requested, an increase of $2 million over last year.

ANIMAL RESOURCES

The requirements of the biomedical scientific research community for increasing numbers of high quality laboratory animals are growing at a rapid rate. The DRFR is attempting to satisfy their needs: through creation and continuing support of certain types of animal colonies; through research into the diseases of the laboratory animal; through development of improved techniques for animal husbandry and colony maintenance; and, perhaps most importantly, through training of a cadre of animal-care specialists capable of exploiting to the fullest the potential inherent in the present and future animal facilities and resources of the country.

PRIMATE CENTERS

The national and regional primate research center program, administered by this Division, is now firmly established. With the dedication of the New England Regional Primate Research Center in November 1966, the construction phase of the primate center program closed. All of the seven centers originally authorized are now in operation and their research programs underway. The normal biology of each species of primate, including its natural history from conception to death and its intercurrent diseases, is under intense investigation. In addi-

tion, primates are being used in the centers for research in genetics, infectious diseases, reproductive biology, nutrition, aging, and drug testing, plus a myriad of other studies.

To provide continuing support for the ongoing research programs of these centers and to permit fuller utilization of the facilities made available by the completion of construction, $10.5 million is requested for fiscal year 1968, an increase of $1.5 million over the funds appropriated in fiscal year 1967.

NON-PRIMATE ANIMAL RESOURCES

In addition to the need for subhuman primates, other species and strains of laboratory animals are required in large numbers and of high quality. The animal resources program of the DRFR provides assistance to grantee institutions to improve the care and welfare of research animals, for research projects in laboratory animal medicine, and for the establishment and maintenance of colonies of animals particularly useful in research.

To support 41 ongoing grants, and an estimated 10 new grants for animal resources which would include support for renovation of institutional facilities to meet new standards, $5.1 million is requested for fiscal year 1968. This represents increase of $2 million over fiscal year 1967.

SPECIAL RESEARCH RESOURCES

The special research resources program provides funds to establish and to operate the large-scale, highly specialized instruments and instrument systems that are increasingly necessary for the prosecution of modern research. Resources of this character are usually centralized within a single institution and provide services to a wide scientific clientele both in that institution, and, frequently, in neighboring institutions. First given explicit organizational status in 1962, this program now supports 59 such centralized resources, including 43 biomedical computing centers. Other classes of resources within the program are centers for analytical biochemistry instrumentation, for biological materials production, and for scientific and technical information.

Computational facilities funded by the program serve biomedical science in numerous ways. They assist scientists with special problems that call for data collection, processing, and analysis on a massive scale. They can continuously monitor certain types of research experiments and automatically modify them. They assist in the solution of some of the complex differential equations describing the physical and chemical characteristics of biological systems. They make possible the construction and the rapid manipulation of mathematical descriptions, or "models," believed to characterize the behavior of living systems. And they provide very rapid access to sources of previously stored data and information.

In one special research resource, investigators appear to have successfully solved the problem of teaching a machine to recognize the pattern of ventricular activity in the electrocardiogram, not only under normal circumstances—a relatively easy task—but in a wide variety of pathological conditions. This is a major step toward detection by machine of abnormalities in heart rhythm. These techniques make

it possible to collect and rapidly analyze comprehensive quantitative data on the electrical behavior of the heart following myocardial infarction. These studies are being extended to develop devices that can automatically alert the physician if undesirable events are taking place. When investigations made possible by this technique have been completed, information will become available to enable physicians to select better criteria for triggering the alerting alarm.

To provide continuing support for the special research resources program, $10.8 million is requested for fiscal year 1968, the same amount as that requested in 1967.

GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES

This concludes the elements in the "General research and services" appropriations administered by DRFR. We move next to our health research facility program which has a separate appropriation and is depicted in yellow on the chart before you.

The health research facilities construction program, authorized under part A of title VII of the Public Health Service Act, began its second decade of operation in the present fiscal year. The objectives of the Hill-Bridges authorization, which has been renewed four times, were to expand the total national "plant capacity"—the physical facilities—for health research through the construction of new, the renovation of outmoded, and the replacement of obsolete research facilities.

In cold statistical terms, the program has awarded 1,383 grants over the past decade, totaling $396 million. These were distributed among 405 different institutions in every State, as well as in the District of Columbia and Puerto Rico. Upon completion, these projects will have provided for the construction or renovation of more than 17 million net square feet of functional modern research space. Grantee institutions have more than upheld their end of the partnership, matching the Federal contribution of $396 million with $550 million from non-Federal sources, thus substantially exceeding the statutory requirement of contribute 50 percent of the cost.

But the real measure of the accomplishments of this program is not the dollars spent, nor the square footage of space built or renovated, nor the number of laboratories equipped, nor even the number of scientists housed. Surely, the true and meaningful measure of this program is the progress that medical science has made in the war against disease, disability, and death. And it is abundantly clear that this program has contributed, directly or indirectly, to the prosecution, during the last decade, of a very large number of important research projects which can be credited with advancing the treatment of cancer, with the control of infectious diseases through chemotherapy or by immunization with vaccines, and with the amelioration of metabolic diseases. Most of these projects could not have been undertaken unless this program had provided the laboratories in which biomedical research scientists, young and old, could work.

The research achievements already made possible through the construction of health research facilities constitute incontrovertible testimony to the past value of this program. But what are the needs of the present, the issue before us here today? Medical science has come

a long way, but there is still much to be learned, understood, probed. Bright young people are emerging from training, eager to join their preceptors in seeking solutions to the problems and challenges of disease. There simply isn't enough space available for them to work. All classes of research space are in short supply, a fact that plays a key and controlling role in the ability of the Nation to get on with the task of discovery, so essential to achieve dominion over disease and death. The biomedical research institutions of the Nation need new research space, to relieve the crowding of existing facilities and to provide suitable accommodations for their expansion. They also need to modernize research space that has become less than optimally useful. Today, as a result of the rapid pace of scientific progress, the same premise holds true for laboratory design as it does for men and ideas: be renewed or wither. The new medical schools, which must be created to expand the number of physicians needed to provide medical care to our people, must have research facilities if they are to attract competent faculties. Finally, the enactment by the Congress of Public Law 89–544, regulating the transportation, sale, and handling of certain animals intended for use in research, has focused attention upon yet another facet of this problem. This act has made even more immediate the realization that the biomedical scientific research community has had only limited success in providing facilities for laboratory animals at a rate commensurate with the growing use of these animals in medical research programs.

For fiscal year 1968, $35 million is requested to help meet the needs of the health research facility program.

GENERAL RESEARCH SUPPORT

The general research support program, created by Public Law 86–798, was explicitly designated to strengthen institutions. 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.

FORMULA GRANT PROGRAM

The first administrative device used to take advantage of this authority for the general support of research and research training was a formula grant program. Schools of medicine, dentistry, and public health were the initial recipients of awards. Later, qualification requirements were extended to include other health professional schools; to hospitals engaged in research; and to State and municipal health departments for research programs.

In the spring of 1966, at the urging of Congress, this formula grant program was extended to include nonhealth professional components of the graduate divisions of academic institutions. The new program, together with its predecessor, provides proportional funding for re-

search and research training to institutions heavily engaged in the type of health-related research that is of interest to the NIH.

These two programs deliberately permit and encourage institutions to exercise broad discretion in the use of the formula 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 creatively administer grant funds 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 mission 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.

There can be no question that these two formula grant programs have served as a powerful instrument to help institutions throughout the Nation strengthen and expand their health-related research capabilities.

COMPETITIVE DEVELOPMENTAL GRANTS

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 interest of the entire Nation.

During the past year, the NIH announced a new program to encourage comprehensive institutional advancement toward excellence in biomedical research and research training. Called the Health Sciences Advancement Award, it will provide grants to carefully selected colleges and universities that can demonstrate evidence of growth potential in health-related research activities. Funds from this program will be directed toward institutions that can become truly centers of excellence in research and research training by developing their facilities, staff, and research potential.

The first nationally competitive cycle for Health Sciences Advancement Awards is now underway. With these new awards, we hope that more and more outstanding health science research centers will emerge throughout the land to help conquer disease.

The President's budget requests $61.7 million for fiscal year 1968, an increase of $10 million, for this complex of programs, as follows: $43.2 million for the traditional general research support program; $7.5 million for the biomedical sciences support grant program; 11 million for support of the Health Sciences Advancement Award program.

In summary, Mr. Chairman, I am pleased to support the President's request for a total of $158,714,000 for the Division of Research Facilities and Resources. This includes: $62,014,000 for clinical, animal, and special research resources under the General Research and Service appropriation; $35 million for grants for the construction of health research facilities; and $61.7 million accrued by transfer from the budgets of the categorical institutes for general research support.

Mr. NATCHER. Dr. Kennedy, we want to thank you for your statement.

I have a number of questions that I would like to ask concerning the matters that have been called to our attention this morning, but before taking up these questions I am going to yield at this time to Mr. Laird.

ORGANIZATION AND APPROPRIATION STRUCTURE FOR GENERAL RESEARCH AND SERVICES

Mr. LAIRD. Dr. Shannon, I cannot understand this operation you have here. It does not look like very good budgeting to have such a disparity between the appropriation structure and your organizational structure, and also your basic legal authorities.

Maybe we have not gotten into this in the past as thoroughly as we should, but I did not realize this was so mixed up.

Dr. SHANNON. Mr. Laird, we presented an organizational chart at this time particularly because of the difficulty we had in explaining the interrelated activities to this committee last year.

If I may speak from the chart, I would point out that if one looks at the institutions as institutions, then these three activities relate one to the other as a functional entity, although they derive their authority from three different public laws and three different authorities.

The activities which are combined in the general research and services are isolatable activities. One is largely of a staff nature; namely, that of the Office of International Research, while the others are of an operational nature in support of the direct operation.

If you look to the appropriation history, you may recall that we have progressively tried to clarify this complex situation. Some years ago we removed from this appropriation the Division of Research Grant activity and later the National Institute of General Medical Sciences. Two years ago we also removed from this appropriation the Division of Biologics Standards. These now come before you as separate and independent activities.

I would think it is highly in order, when the present authority for health research facilities construction runs out and Congress is approached with a request for new authority next year, that this entire appropriation structure be looked at from the standpoint of how and under what authority it is best possible to pursue these institutionally oriented activities.

But meanwhile the thing that makes it very confusing to the committee is that if one attempts to portray, in a rather rigid budget schedule, the various activities contained under various authorities, then one loses this functional grouping that is possible through these administrative techniques.

From the standpoint of the performance of the function, Dr. Kennedy's operation, while it makes use of three authorities, is conducted as a single operation. Computer research and technology is conducted as a single divisional activity. The Office of International Research is the extension of my office into those areas of NIH concern in the international field.

INTERNATIONAL CENTER

Mr. LAIRD. Something certainly should be done to better organize the appropriation structure.

Will some of the activities of the Office of International Research be transferred to the new International center?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. How much will be transferred?

Dr. SHANNON. Mr. Laird, should it be enacted that we undertake the establishment of an international center, many programs of the Office of International Research will be transferred to it.

Mr. LAIRD. It will all be there?

Dr. SHANNON. There are certain elements that will not conveniently go into the Center, at least as we have proposed it to the Department, but which can be distributed back to the Institutes. We would not have anything other than a small staff group that would serve as an intelligence unit for the Office of the Director of NIH to exercise surveillance over the various elements of the international program, but the Office of International Research, as you see it today, will be considerably changed.

GRANTS TO CLEVELAND CLINIC

Mr. LAIRD. Where are grants to the Cleveland Clinic made?

Dr. SHANNON. We make many grants to Cleveland Clinic, Mr. Laird.

Mr. LAIRD. I thought it was under the formula grant program you made grants to the Cleveland Clinic.

Dr. KENNEDY. They might qualify as a recipient of general research support if they had applied. There are a total of about 290 traditional general research support grants made and approximately 100 biomedical sciences support grants; individual ones, that is.

Mr. LAIRD. I am looking here at your statement on page 10, and you list professional schools, hospitals that are engaged in research.

Dr. KENNEDY. Correct.

Mr. LAIRD. Is this limited just to these?

Dr. KENNEDY. Grants are awarded to components of institutions. The first grants were made to academic institutions. Under academic institutions we supported, originally, schools of medicine, schools of dentistry, schools of public health, and schools of osteopathy.

Eligibility was later enlarged to include other components: schools of veterinary medicine, schools of pharmacy, and then extended to include research institutes like the Worcester Foundation, and hospitals such as the Massachusetts General, and the Peter Bent Brigham; and finally to State and municipal health departments.

Mr. LAIRD. I do not see where it includes foundations.

Dr. KENNEDY. This is not an exhaustive list of the components.

Mr. LAIRD. You support the same kind of activity out of several of these appropriations, do you not?

Dr. SHANNON. No. The activity you have in mind specifically in relation to the Cleveland Clinic Foundation would be in this general research support grants activity. If they came to us—as a nonprofit agency incorporated for special purposes to expand their physical resources, they could apply for a research facilities construction grant.

Indeed, if they came to use to expand their animal resources, they could apply for this type of grant.

Mr. LAIRD. You are all through the construction phase?

Mr. KELLY. We are through with construction. We are continuing to support them.

Dr. SHANNON. The important thing is that this activity pays little attention to the individual scientists. It is primarily oriented toward the resources of the institution which contains the scientists.

"FORMULA GRANT" DEFINED

Mr. LAIRD. Could you explain to me the term "formula grants"? I still do not understand this term "formula grants" as it is used in reference to this.

Dr. SHANNON. When we justified this authorization before the Congress we pointed out that the need for a general type of support increases as the complexity of the scientific programs in an institution increases. A modern science has developed, and particularly in the biomedical sciences, funds derived from private giving, from voluntary associations such as the American Heart Association and the American Cancer Society, or from our own support, come to the institution for specific projects and for specific purposes.

We felt at that time, and the Congress agreed, that there were certain things of great importance to the institution that could not be accomplished by project grants, and that is why the Congress created the general authority.

What the formula attempts to do——

Mr. LAIRD. Tell me what it attempts to do.

Dr. SHANNON. It attempts to express, in terms of dollars, the complexity of the program at the institution.

Dr. Kennedy can give the elements of it.

Mr. LAIRD. What is the formula?

Dr. KENNEDY. The formula is a proportional formula. In other words, the size of a general research support grant to an institution is proportional to the total amount of research grant dollars that they expend both from NIH grants and from non-Federal sources.

In other words, it is a kind of a "surgrant" on top of and proportional to research project grant support.

Mr. LAIRD. Is it percentage, or how does it work?

Dr. KENNEDY. It is based on the expenditures that an institution makes. An institution receives a grant of 10 percent on the first million dollars of non-Federal research expenditures in a given year.

In addition to this, it receives an additional 6 percent on the second million dollars of non-Federal expenditures. It receives 5 percent on the first million dollars of Federal research expenditures and 3 percent on the second million dollars of Federal expenditures. It is, thus, a tapering formula with a sharp cutoff. Institutions get no credit for research expenditures in excess of the $2 million from Federal and non-Federal sources.

Additionally, health professional schools receive a base grant of $25,000.

MINIMUM RESEARCH LEVEL REQUIRED

Dr. SHANNON. In order to qualify, there must be a minimal amount of research activity both as to dollar value and diversity of the program prior to qualification.

Dr. KENNEDY. The threshold of support requires that an institution, to be eligible for this award, receive $100,000 of NIH grant support of a diversified nature.

Mr. LAIRD. But any institution that is receiving $100,000 worth of Federal funds gets this blanket grant which you call the formula grant?

Dr. KENNEDY. Correct; if the institution applies for an award and if staff and council recommend it.

Mr. KELLY. These funds are restricted. You understand, Mr. Laird, that they have to be used for the conduct of authorized and allowable projects in the research and training field.

Mr. LAIRD. Not approved by anybody, though?

Dr. KENNEDY. Not as individual projects; that is correct.

Mr. LAIRD. This is sort of a free fund you are giving them.

Dr. KENNEDY. It is for research and research training activities for which the decisions and the judgments are made by the institution. It is postaudited by our staff to make sure that these indeed were health research and research training expenditures.

Mr. LAIRD. This has gotten to be quite a sizable program.

Dr. KENNEDY. In the authorizing legislation a ceiling of 15 percent of the aggregate budget of the National Institutes of Health for research project grants was established.

Dr. SHANNON. I might say, Mr. Laird, in the initial presentation of this program to the Congress, our proposal was that during the initial year the expenditures under this program would be limited to 5 percent of the total research grant funds for the various Institutes.

The second year it would be limited to 10 percent and the third year it would be limited to 15 percent. Not only limited, but those would be the objectives.

In our discussion of it, we said that we felt that, after one reached the 15 percent, or approximately that, in the third year, it should be held at that level for a period of some 3 or 4 years. A general decision should then be made as to what proportion of the total grant funds might best be expended by the use of these techniques rather than through individual project grants.

In point of fact, we have not felt it advisable, within the budgets available to us, to move as rapidly as we had indicated to the Congress we proposed to do. At the present time, I believe that the percentage of research grant funds used for general research support grants is 8 or 9 percent.

EXCLUSIONS FROM ENTITLEMENT TO GENERAL RESEARCH SUPPORT GRANTS

Mr. LAIRD. How does this work out where you have an institutional grant?

Dr. SHANNON. This is an institutional grant.

Mr. LAIRD. Where you have a big institutional grant for, say, a cancer center or a heart center. Do they get a percentage on that, too?

Dr. KENNEDY. Yes.

Dr. SHANNON. There are certain exclusions.

Mr. LAIRD. Let's have the exclusions. You take the center with a big institutional grant, does he get a percentage on this, too?

Dr. KENNEDY. We exclude things that are regional rather than institutional resources.

Mr. LAIRD. That is not what I am talking about. Are they excluded or are they not?

Dr. KENNEDY. They are.

Mr. LAIRD. And none of those people get any of this money?

Dr. KENNEDY. They get it for their regular project grant support.

Dr. SHANNON. They would not get it for a regional center. Also, under the new arrangement with Sloan-Kettering, where we negotiate a single instrument for all NIH support, they will get none. But any grant that goes to an institution primarily for institutional purposes is included in the formula.

Mr. LAIRD. One like Sloan-Kettering gets none of these funds?

Dr. SHANNON. No, sir.

Mr. LAIRD. Let's take Dr. DeBakey's program. Will that qualify?

Dr. SHANNON. He has now completed construction of a cardiovascular research unit and he has discussed with us the funding of this cardiovascular research unit. I believe it comes into being, Mr. Casey, within the next few months, does it not?

Mr. CASEY. That is my understanding.

Dr. SHANNON. When we negotiate with him, we will negotiate on the basis of the overall support of that activity and make an agreement with him comparable to the one we have now made with Sloan-Kettering. That money will be removed from competition for funds under this formula. Perhaps a narrative statement would clarify the record on the types of grants and expenditures that are excluded from entitlement to general research support grants.

Mr. LAIRD. I think this is poor use of the term. Formula grant is misleading.

Dr. SHANNON. You are right.

Mr. LAIRD. The purpose here is to make general support available so these schools have a little free financing to decide to do some research on their own.

Dr. SHANNON. This is correct. You are perfectly right, it is not a formula grant. This grant is so restricted, from the standpoint of what can be done and what cannot be done with the funds and how it is administered, that it does, indeed, depart from the concept of a formula grant such as is made to States in support of a public health function. There is no relationship to such an operation.

I might say to that, automatic eligibility under the guidelines of this does not necessarily mean automatic payment because each of these grants is reviewed by the Council in light of an institution's program and what additional funds can be expected to do. Many institutions, which would get grants if this formula were applied in an automatic fashion, are judged by the Council not to have a program of such complexity or diversity as to warrant this type of support.

(The following statement was subsequently submitted:)

In determining entitlement to General Research Support grant awards, the following types of grants and expenditures are excluded by the published guidelines governing the program:

1. Funds that were not specifically restricted for health-related research by the donor at the time of the tranaction;

2. Multiple-purpose awards, even though health-related research was one of the purposes. If the funds may be used to support health-research training, medical treatment, or construction activities, they are considered multiple-purpose awards. If, however, at the time of the transaction the donor identified a portion of such funds for use only for health-related research, expenditures up to the amount so identified may be included;

3. Public Health Serivce General Research Support Grants, Biomedical Sciences Support Grants, Health Sciences Advancement Awards, and Regional Medical Program Grants;

4. Grants, contracts, and awards for education, research training, research fellowships (including supply grants), research career development, construction, conferences, meetings, and scientific review and evaluation grants (commonly called chairman's grants);

5. Health services formula and demonstration grants;

6. NIH-sponsored regional research resource centers. Such centers as primate and other animal facilities, computer centers pharmacology-toxicology centers, and instrument development centers are considered to be "regional" in nature if the services of the center, as indicated in the approved application and subsequent award, are intended for utilization beyond the grantee institution;

7. Professional fees charged by staff members of the institution for professional services or care, or royalties which are returned to the institution as an additional source of institutional health-related research funds earned by staff members on patents on inventions. This restriction is made because these funds are considered to arise from "inside" the institution and only expenditures from funds from "outside" sources may be included.

Grants to institutions for clinical research centers are included in computing General Research Support along with expenditures from health-related research projects and contracts.

In the case of the Sloan Kettering Institute, where a single large grant for all NIH support has been negotiated, the terms of the agreement specify that funds for General Research Support will be terminated at the end of the current grant year. General Research Support funds from the Division of Research Facilities and Resources were provided during the transition period when the Sloan Kettering Institute changed from conventional support from NIH to this new mode of support.

JAPANESE-AMERICAN RESEARCH PROGRAM

Mr. LAIRD. One more question. I am still trying to corroborate the memorandum that the Association of American Medical Schools sent out on the contribution that is being made to some of these international projects, like the one with Japan. The memorandum which I got indicated that there was no contribution made by the Japanese Government.

Dr. SHANNON. That is not correct, sir.

Mr. LAIRD. Then there is a contribution?

Dr. SHANNON. Yes, sir.

Mr. LAIRD. How much is it?

Dr. SHANNON. I will have to try to find out.

(The information follows:)

The Japanese Government supports institutions and investigators involved in the Japanese program with a direct appropriation of $245,000.

Mr. LAIRD. We are granting about $4.5 million.

Dr. SHANNON. At the present time, yes.

Mr. NATCHER. Mr. Smith?

HEALTH SCIENCE ADVANCEMENT AWARDS

Mr. SMITH. Regarding these general research support grants, I guess you would call them formula grants.

Dr. SHANNON. We will not any more, sir.

Mr. SMITH. As I understand it now, you are asking to take some of the money, and you did last year, that was available for those kind of grants and use it for some special grants that you call Health Science Advancement Awards.

Dr. KENNEDY. Correct.

Mr. SMITH. Last year you had eight of these and now you are proposing to have 22 next year. I notice these total $500,000 each. Are they each one equal in amount or are they different amounts?

Dr. KENNEDY. No, they are not. Let me say we have made no awards as yet from this year's funds, sir. The first nationally competitive cycle began in July 1966. The preliminary screening of applications went through September and October. We invited 15 institutions to submit the full scale proposals in late November or early December. These latter proposals were received about the first of March 1967. Our staff has been very busy in an analysis of these and in making site visits at these 15 institutions. They will come before a preliminary review group in May and before the June meeting of the National Advisory Health Council. So none of these have been made. It is our guess that about half a million dollars is probably the right order of magnitude for this grant.

Mr. SMITH. So then you do not have the list of the eight available?

Dr. KENNEDY. We do not.

Dr. SHANNON. We can give you the list of the ones that were selected.

Mr. SMITH. The 15?

Dr. SHANNON. Yes. Could I make one point before we close that?

Dr. Kennedy did not point out that in general our project system is not suited to develop competence and excellence where excellence does not already exist.

Mr. SMITH. What is your legal authority for these new type grants? This is a general support program, isn't it? You are supposed to have uniform grants. How can you take part of the money and make some special grants? That is not uniformity any more, is it?

Dr. SHANNON. No, sir. The uniformity relates to the derivation of the funds. There is broad authority in the legislation to deal with institutions in support of research and research training. It is under that authority that these grants are made. It is under this authority that we propose to attempt to develop a more equitable distribution of scientific excellence within the Nation.

Mr. SMITH. Your authority in section 301(d)?

Dr. KENNEDY. Section 301(d) as amended by the Public Law 86-798.

Mr. SMITH. Wasn't that legislation for the purpose of providing funds for continuing the formula basis grants, continuing grants?

Dr. SHANNON. Sir, it is broader than that. That is the first element that we activated.

Mr. SMITH. Have you gotten any opinion from your general counsel that you can have special grants under this legislation?

Dr. SHANNON. I believe so; yes.

Mr. SMITH. Would you place that in the record?

Dr. SHANNON. Be very glad to, if it is available.

(The information follows:)

Review of the history indicates that NIH did not at the time of the initiation of the program consider it necessary to seek a formal legal opinion on the question raised. This judgment was based on informal discussions which NIH had with the Office of the General Counsel concerning the coverage of the Act, prior to the initiation of the program.

We have again reviewed the legislation and continue to believe that it provides the authority for this program. However, in response to the wishes of Congressman Smith, we will submit a request to the Office of the General Counsel for a formal opinion and provide the subcommittee with a copy when it becomes available.

APPLICANTS FOR NEW HEALTH SCIENCE ADVANCEMENT AWARDS

Mr. LAIRD. Why not have him put the names of those 15 institutions into the record?

Mr. SMITH. Yes.

(The information follows:)

CANDIDATE APPLICANTS FOR NEW HEALTH SCIENCE ADVANCEMENT AWARDS FROM INCREMENTAL FUNDS ($3.0 MILLION) IN F.Y. 1967 BUDGET

1. Florida State University, Tallahassee, Florida.
2. Rutgers, The State University, New Brunswick, New Jersey.
3. Purdue University, Lafayette, Indiana.
4. Rice University, Houston, Texas.
5. University of Oregon, Eugene, Oregon.
6. University of California, San Diego, California.
7. Carnegie Institute of Technology, Pittsburgh, Pennsylvania.
8. The University of Rochester, Rochester, New York.
9. Vanderbilt University, Nashville, Tennessee.
10. Brown University, Providence, Rhode Island.
11. University of Colorado, Boulder, Colorado.
12. State University of New York, Stony Brook, New York.
13. University of Vermont, Burlington, Vermont.
14. Washington University, St. Louis, Missouri.
15. University of Tennessee, Knoxville, Tennessee.

Dr. SHANNON. The point I meant to make is that during the initial year we negotiated with a very limited number of institutions that were knowledgeable about the program from reading the congressional hearings and from correspondence with us. We selected four, initially, for pilot studies of how these grants could best be developed to satisfy the purposes for which they were designed. We actually negotiated in great detail with three for these establishments, ultimately, two awards were made in fiscal year 1966. On the basis of the knowledge we acquired during that initial exercise, we were willing to open it up for national competition.

Knowing that the needs were so great and so highly diversified, we requested that institutions not submit detailed formal applications because the funds were limited and we knew that very few could be granted. We requested, instead, quite detailed letters of intent with enough information so that the programs proposed could be visualized by the advisory group.

Mr. SMITH. Are all of these educational institutions?

Dr. KENNEDY. It was limited to educational institutions.

Mr. SMITH. So in effect what you really have in this program is some Federal aid to education without a formula.

Dr. KENNEDY. No, sir. Educational institutions primarily because they are the source of scientists and the awards are for science research or for science training. We felt that in order to develop strong institutions, it would be better to focus on those that had an educational capability, particularly in the field of graduate education, rather than simply to support, by fluid funds, research institutes. We feel that we have other means of doing that.

Mr. SMITH. Now you are proposing to have grants, special grants to 22 institutions within the 1968 fiscal year. Will the eight that are getting it this year be included in the 22?

Dr. KENNEDY. Yes. We are proposing that the incremental funds support 14 new institutions. On the other hand, it is our view that the

period of each of the grants should be for 5 years. So that the existing base of support, which is $4 million in this year's budget, will continue to support for the next 5 years those institutions which receive awards this year.

Mr. SMITH. I am not clear. Do you mean the eight, then, would automatically be included within the 22 or automatically excluded?

Dr. KENNEDY. The 22 include these eight.

Mr. SMITH. But the eight would also receive a grant again?

Dr. KENNEDY. Correct.

Mr. SMITH. In the same amount?

Dr. KENNEDY. The amounts for the first 2 years are established by Council recommendation. The size of the grant for the next 3 years will be negotiated with them on the basis of the utilization of the funds to date.

LEGAL AUTHORITY FOR THE GRANTS

Mr. SMITH. Are you sure you have a legal opinion that this is permissible within this authorizing legislation?

Dr. SHANNON. Quite frankly, Mr. Smith, I am not certain. I know we have discussed this extensively with the General Counsel. I believe we have an official opinion and this we will put in the record.

Mr. SMITH. It should be interesting. I do not see how he can hold that those grants are authorized under 301(d). It seems to me you are on a whole new program. What you are really doing is diverting some general funds from the general support area and from the 310 institutions and picking out some and giving them a bonus, which in effect reduces the others. I mean, there is only so much available.

Dr. SHANNON. Yes. The primary program purpose of this is to permit the more rapid evolution of centers of excellence.

Mr. SMITH. I am not saying whether it is desirable or not desirable. If it is desirable it seems there ought to have been a considerable amount of backup material and planning for it. Of course, it would have to be within the legal authorization.

ANIMAL CARE SPECIALISTS

Would you explain this "Cadre of animal care specialists," what you contemplate, what the cost is, and how many people are involved?

Dr. KENNEDY. There are essentially two programs. One is a program of training grants. These will be primarily, as most NIH research training grants are, directed at the early postdoctoral training of young veterinarians in formalized training programs in which there is competition among universities for the funds to set up the programs.

Mr. SMITH. Are these to be employees?

Dr. KENNEDY. Oh, no; these will be training programs established under a principal investigator in universities throughout the country. This program will be responsible for taking young veterinarians, clinically competent in veterinary medicine, and giving them a new dimension of training so that they can work effectively in a research environment and be the people who will run the very large and elaborate animal facilities that exist in many biomedical research institutions.

Mr. SMITH. It may be better if we use a specific example. Now, Iowa State University has a veterinary school and they have a very extensive school on pets, and so forth. Now, what will this do with regard to them?

Dr. KENNEDY. Well, it would be our view that these training programs would take the graduates from that school who are competent in veterinary medicine.

Mr. SMITH. Some of whom have already specialized in pets?

Dr. KENNEDY. Well, our focus is on laboratory animals, those animals which are used commonly in biomedical research—rats, mice, guinea pigs, hamsters, rabbits, pigs, miniature pigs, dogs, cats, subhuman primates, chimps, and so forth. These people would learn in these training programs what has to be known to enable them to assume responsibility for the very extensive animal research resources needed by institutions heavily engaged in medical research. For instance, in NIH's own direct operation, there is an enormous amount of space on campus for laboratory animals and, in addition, we have a very large farm out in Poolsville where animals are held.

I think that the pattern that is emerging around the country is is quite similar. Most medical schools, for instance, are developing very extensive central facilities for their laboratory animals and in addition, sometimes individually and sometimes through consortia of institutions, they are developing farms in rural areas. We want to train the people, by both fellowship and training grant programs, to take responsibility for this. They need to know a great deal about the special problems of the laboratory animals, the special diseases of the laboratory animal, the special nutritional requirements, and so forth, to run these well.

Mr. SMITH. Are you saying that the vets that have been available for these kind of jobs have not been competent to handle these jobs?

Dr. SHANNON. Might I comment on that, sir? That is correct. Most veterinary schools have as the major outlet for their graduates the field of agricultural needs or the care of pets. Now, when you take one of those people into the biomedical sciences they encounter problems of diseases that are quite different, problems of containment and problems of the experiments themselves and the capability of different animal forms to be utilizable in those situations.

Mr. SMITH. How long a period of time will one of these fellowships be for? What is the cost?

Dr. KENNEDY. The period of training for young people, and these training programs are young graduates, may be from 1 to 3 years. I might say there is a parallel here with the young physicians, that is to say, physicians who are going into research also participate in the training programs supported by other Institutes of NIH. The stipends in these training grants are $5,000, $5,500, and $6,000 depending on the year.

Mr. SMITH. Per year?

Dr. KENNEDY. Per year. There is a dependency allowance and a maximum tenure on a training grant of 3 years. In addition, the institutions would get some funds.

Mr. SMITH. How many would there be?

Dr. KENNEDY. Well, we are planning through the training grant programs in the projected budget that 30 individuals will initially be included.

Mr. SMITH. Do you select the individual?

Dr. KENNEDY. The training grant mechanism is one under which the institution selects the individuals. We select the institution for the training on the basis of competitive application. On the other hand, once the training institution has been selected, the individual trainees for the program are selected by the institution. In the fellowship programs we make the selection.

Mr. SMITH. Would these recipients be under a contract or under some legal obligation to work in this kind of a center or with primates in research facilities after they arrive?

Dr. KENNEDY. No formal obligation.

Mr. SMITH. Then they might just become a pet specialist in New York City or somewhere.

Dr. KENNEDY. Well, it will not do them much good, this kind of training.

Mr. SMITH. All these things are pets any more, monkeys, dogs, cats, guinea pigs.

Dr. SHANNON. Mr. Smith, I doubt it. Our own experience has been that veterinary practice in the field of pets is certainly a highly lucrative enterprise.

Mr. SMITH. It is, yes.

Dr. SHANNON. All I can say is that it is highly unlikely that a graduate from a veterinary school would move into this area for training of 1, 2, or 3 years to acquire experience that will have no value in the care of pets. He must be motivated to this type of area before he comes in. On the other hand, I think it would be most unwise to impose an obligation that he must take a position in the science area as a condition of his entering training for two reasons: One, it may well turn out that he does not have the qualities, the qualifications, or the competence to be effective and, two, in general, I do not think indentured labor is very wise.

Mr. SMITH. A pet specialist may make $40,000 to $50,000 per year. What makes you think he is going to go into one of these institutions for $25,000?

Dr. SHANNON. A person who has that kind of salary available isn't going to accept a stipend at the $5,000 level. He isn't going to reenter the academic environment for a period of 1, 2, or 3 years if his motivation is primarily to be a pet specialist at a very high salary.

Mr. SMITH. After 3 years of this he will certainly be in a position to get more money as a pet specialist, will he not?

Dr. SHANNON. I do not believe so, sir, because the experience he will have as a result of that 3-year training will be knowledge of a wide variety of diseases and epidemic diseases of small animal colonies, he will be knowledgeable about the problems of animal containment, he will be knowledgeable about the problems of animal breeding for scientific purposes in relation to the scientific needs of laboratories which certainly are different than the pet field.

Mr. SMITH. There would have to be a heavy emphasis on his ability to deal with diseases of each one of these primate animals.

Dr. SHANNON. Yes.

Mr. SMITH. That is exactly what they sell their services for as pet specialists.

Dr. SHANNON. It would just be my judgment that relatively few will go into that. That is the best I can say.

Mr. NATCHER. The committee will adjourn until 2 o'clock.

Mr. NATCHER. The committee will come to order.

SUMMARY OF BUDGET REQUEST FOR GENERAL RESEARCH AND SERVICES

First, under "General research and services," I notice the adjusted appropriation is $71,968,000 and the request for 1968 is $81,141,000, which is an increase of $9,173,000.

INTERNATIONAL ACTIVITIES

The big increase is for research grants, $7,739,000, and $2,489,000 of this amount is for an increase of about one-third in the international field. Now, as you know, Dr. Shannon and Dr. Kennedy, research is becoming suspect in some quarters and international activities have been for some time in this category.

What else would you like to say in regard to this particular increase? Is it absolutely necessary at this time?

Dr. SHANNON. Well, sir, let me discuss the specific program in the international field first.

This was discussed at length with the Bureau of the Budget in arriving at these estimates, primarily in terms of the program content of what we propose to do; in part in relation to our own domestic objectives; and in part in relation to the way in which these activities will make available information about health problems in critical areas of the world where other approprations address thmselves to other problems. I have primarily in mind DOD and AID, of course.

This figure was arrived at, in conjunction with the total figure for research grants that we were allowed to request, as part of the total program. These funds will be used to support American scientists in programs of general concern to the American people. Administratively they will be pulled together in such a fashion as to serve the dual purpose of making information available not only for domestic purposes but also for those purposes that we have abroad, particularly in Southeast Asia.

The program content relates to very broad domestic programs. I have mentioned tuberculosis and leprosy. Leprosy is a minor problem in most areas and is, perhaps, only important in Puerto Rico. But these two diseases are so related, one to the other, that it is very useful to study them together.

INSECT-BORNE VIRAL DISEASES

The second area of deep concern is the so-called insect-borne viral diseases. These are of grave consequence to the United States. We are expending substantially more than this amount in the general program on these problems. We are expending a substantial sum in Panama. Panama serves as a land bridge, it serves as a bird flight area, where a number of diseases transmitted from north to south in the hemisphere tend to converge. It is an ideal location to study some of these diseases in their more common habitat.

For example, we see each summer epidemics of equine encephalitis, eastern encephalitis, St. Louis or mountain or western encephalitis. These are diseases that invade in epidemic form. It is true that they are mainly important economically, to our cattle and horse industries, but they do spill over into the human population. Then they withdraw at the end of the infection season and tend to disappear from the United States as a continuing year-round type of infection. It is our attempt to understand the movement of diseases such as this that makes these general studies of very broad relevance.

NUTRITION STUDIES

We spoke at some length, in relation to the child health appropriation, about a program in Guatemala that attempted to relate certain problems of nutrition to problems of human development. In the Japanese-American program there is a somewhat parallel study that is planned for Chiang Mai, which is north of Bangkok, where a somewhat analogous situation will be studied, where the relationships of poor protein nutrition, and perhaps dietary deficiencies in vitamins and the like, complicated by infection and parasitism, lead to broad problems in human nutrition.

It is possible to study these problems in a definite manner in isolated populations of this sort—in specific villages—which it would be quite impossible to study in this way in our own country.

We have problems of food supplementation in which this Nation is quite heavily involved, at the present time, through the school lunch program, in an attempt to get food to the so-called urban poor or, indeed, the rural poor. The basis upon which these programs are operated and what can be expected of them assumes that we have a sound general knowledge of what our food needs are. But, indeed, there is very little scientific evidence to show what are the key elements that must be considered in manipulating diets for their general dietary adquacies.

CHOLERA

We feel that studies done outside the United States can provide this type of information much better than is possible in the very complex society in which we live.

Some of the problems in the Japanese-American program are now quite serious problems to our very substantial investment of U.S. nationals in these areas. Cholera is one of these.

Actually, the bulk of the funds that are being spent in cholera research by NIH come from AID funds that are assigned for use in Southeast Asia. Very little of our money goes into it.

As a result of this type of study over the past 4 or 5 years, it now begins to emerge that it is not unlikely that we may come up with a high specific antitoxin.

We have at the present time some 450,000 troops at risk in an area where cholera is not unknown. We have very large commitments in terms of other civilians, both Government officials and those engaged in industrial aid out there. This disease is spreading. It is now fairly extensive in the Philippines, it has been observed in Bangkok, it is now in the Near East, and, indeed, earlier in the history of our own Nation it was in epidemic form in the United States.

So that I think, taking a broad view of national interest, that it makes sense to attempt to bring the modern methods of science to bear on the solutions of this disease and, indeed, the solution would appear to be in sight.

PARASITIC DISEASES

Much the same—talking not so much about the immediate purposes as the general purposes of the United States— can be said of the diseases that come under the category of parasitic diseases. While—malaria, filariasis, or schistosomiasis only affect a small segment of our domestic population—generally, that is, in Puerto Rico—they do constitute very broad threats to the substantial number of Americans who are now working overseas. Our activities in this particular program provide that additional edge that permits some controlled studies that are not possible in the normal range of domestic research-grant projects.

We are talking about a sum of money in the Office of International Research that amounts to about $7.1 million, of which about $5 million is for grants. I do not know our precise figure for research grants in general but it would be, at this stage, something in excess of $600 million. So we are talking about a small fraction of the research grants that we feel will have profound impact both on some of our domestic disease problems as well as some of the problems that U.S. nationals face when going abroad.

Mr. Chairman, I would say research and development is now amounting to a very substantial sum in this Nation. I believe the aggregate sum is about $23 billion, of which some $16 or $17 billion is derived from Federal funds. I think it is very important to realize, too, though, that the funds from the Federal Government going to the support of the type of activity we are discussing here are largely concentrated within the budgets of the National Institutes of Health.

You may recall that I tried to impress on the committee our conviction that when one breaks the general budget down—first into categories, then into the major disease entities that compose the category, then into the major disease—one gets a more accurate picture of the money that is being expended in terms of causation, cure, and understanding the disease. The figures that I presented to the committee, first, for the Heart Institute, then for heart disease and then hypertension, ended up by our allocating $9 million to the study of the causation of a serious disease that affects 15 percent of all adults.

In the past 10 years, as a result of money of that general order of magnitude, it has been possible to develop treatment methods so that deaths due to hypertension have been cut by something like 45 percent in the past 10 years. This permits now the swing of emphasis to causation, in the hope of clarifying causation to provide definitive answers for prevention.

I would be the last one, Mr. Chairman, either to minimize the importance of medical research or to minimize the very broad support that the people, through its Congress, are now giving to medical research.

On the other hand, the problems are great, the stakes are very high, and I think that the very extensive progress, in disease area after disease area, warrants the substantial confidence of the American people in the biomedical sciences.

That is a long statement, sir, but I feel it.

REGULAR PROJECT GRANTS

Mr. NATCHER. You are doing all right, Dr. Shannon.

For your regular project grants you have an increase of $1,653,000 but I notice that $3,744,000 is needed to finance noncompeting continuation grants. So you will actually have to cut back by $2,091,000 on new projects.

Now tell us a little about the type of research that you are conducting here and give us a few examples of some of your worthwhile results. Talk to us about this sizable cutback, Dr. Shannon.

Dr. SHANNON. Yes, sir. That is a combination of research project grants to former international postdoctoral fellows and those program areas that normally would be encompassed within the Japanese-American program. But, if I may confess some confusion, I would like to analyze this further before commenting. As I told Mr. Moyer this morning, I spent some 3 hours in preparing for this and I told him I was sure the committee would be confused because when I finished I was pretty confused.

Mr. NATCHER. Suppose you do, Dr. Shannon, prepare a statement now.

EXPLANATION OF RESEARCH GRANT REDUCTION AND STATEMENT ON UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM

Dr. SHANNON. When it comes to the substance of what is cut out, I would have to refer to the detailed records.

Mr. NATCHER. And in preparing this statement, not only tell about the cutback of the $2,091,000 but also put some details in the record regarding the United States-Japan cooperative program.

Dr. SHANNON. This I would be delighted to do.

(The information follows:)

The question concerning the $2,091,000 reduction relates to a table which shows a net increase of $2,259,000 for research grants. The reduction of $2,091,000 is associated with continuing research grant commitments for two programs with the only significant change occurring in the U.S.-Japan Cooperative Medical Science Program. The table reflects increased needs for continuations of grants awarded in 1967. It also reflects a reduced need for new grants to be initiated in 1968. Although there is a reduction in new grant requirements, the combination of continuation and new reflects a need for a total program increase.

JANUARY 1967.

REPORT TO CONGRESS PURSUANT TO SECTION 5(h) OF PUBLIC LAW 86-610 (THE INTERNATIONAL HEALTH RESEARCH ACT OF 1960)

UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM

General background

President Johnson and Prime Minister Sato, mindful of the many areas of human health which are of great concern to all the peoples of Asia, agreed on January 13, 1965 to undertake a greatly expanded program of cooperation in medical science. As a first step to implement this agreement, they arranged 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 on April 19-21, 1965. This was followed by a Joint Committee Meeting in Honolulu during October 4-7, 1965 and subsequently in Hakone, Japan during August 17-19, 1966. Public Health Service Delegation of Authority Number 118 was granted on May 5, 1966, to authorize the Director, National Institutes of Health and the Chief, Office of International Research, NIH to perform specified functions relating to the United States-Japan Cooperative Medical Science Program.

The scope of the United States-Japan CMS program

The program is concerned with the diseases of great health importance in Asian countries. These diseases or categories of diseases include: cholera, tuberculosis, leprosy, virus diseases (arbovirus, respiratory virus, smallpox, and rabies), parasitic diseases (schistosomiais and filariasis), and malnutrition.

The area of Asia to be considered under the program is not rigidly defined, but it is understood that it may include the Republic of Korea on the north and India and Pakistan on the west, as well as other adjacent countries in the far eastern area.

Primary emphasis will be placed on medical research as the basis for advanced knowledge necessary to effective action. Field research may be undertaken when deemed necessary or desirable.

The program will operate initially within a bilateral governmental framework. Nevertheless, it may involve the participation of scientists of third countries, of appropriate facilities in such countries, and collaboration with international or other organizations.

Organization

The United State 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. A list of the Committee members is attached.

Appointments to Panels have been made by the Director, NIH, and each Panel consists of no more than five members. The period of appointment will not exceed three years and may be renewed. Consultants may be nominated by each Panel for appointment by the Committee in keeping with the scientific requirements. A list of the Panel members is attached.

The Department of State is responsible for the foreign policy and foreign relation aspects of the Program and the Department of Health, Education, and Welfare is responsible for the scientific conduct of the Program.

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 share the costs of the program. Projects of *U.S. scientists will be supported by the United States* and those of the *Japanese scientists by Japan*. The exchange of scientists between the two countries is encouraged as a matter of principle and is to be supported by official or unofficial agencies of either country.

The National Institutes of Health, based on the delegated authority under P.L. 86-610, will provide for the support of scientific projects, will be responsible for the organization, funding, and conduct of all scientific meetings held in the United States, and will provide financial support to the United States Panel members and consultants for attendance at meetings related to the U.S.-Japan C.M.S. Program.

Implementation of the program

In order to discuss and recommend measures to carry out the program agreed upon by President Johnson and Prime Minister Sato, a Joint Planning Meeting was held in Tokyo in April, 1965.

On the basis of the recommendations made at that Meeting to the Government of the United States and to the Government of Japan, the opening Conference of the United States-Japan Cooperative Medical Science Committee and its Panels was held in Honolulu on October 4–7, 1965.

Convened at this Conference were the meetings of the Committee, of the Panels on each of the diseases selected at the Planning Meeting; (a) cholera, (b) tuberculosis, (c) leprosy, (d) certain respiratory and insect-borne virus diseases, and (e) the parasitic diseases, schistosomiasis and filariasis, and the Plenary Session which all the members of the Committee and its Panels attended.

At the Plenary Sessions, the current knowledge on each of the diseases selected at the Planning Meeting was reviewed so as to increase the understanding of all participants regarding these diseases. At the Panel meetings, the development of studies to be undertaken under the Program was discussed as well as more technical aspects of the current knowledge of the diseases concerned. The Committee also agreed to recommend the establishment of a Joint Malnutrition Panel to be added to the list of Panels in the Program.

The second meeting of the U.S.-Japan Cooperative Medical Science Committee was held in Hakone, Japan on August 18–19, 1966.

The meeting proved to be of the utmost importance for the future development of the U.S.-Japan Cooperative Medical Science Program. At this meeting accomplishments during the first year of the Program were reviewed and plans for the research efforts of the Program were discussed.

The Committee formally established a panel on Malnutrition and reviewed the proposed research activities of this panel. The Committee heard reports from the Chairmen of the U.S. and Japanese Panels on (1) cholera (2) tuberculosis (3) leprosy (4) parasitic diseases (schistosomiasis and filariasis) and (5) malnutrition. These reports contained specific plans and recommendations as to the lines of investigation that the panels considered of highest priority. Dr. Edwin H. Lennette, Chairman of the U.S. Virus Diseases Panel, submitted an informal report to the Committee on certain respiratory, insect-borne virus diseases, and rabies.

During the meeting the Committee discussed certain areas of major policy and research agreements as follows:

Since a number of the Panels reported to the Committee the desirability of increasing the exchange of scientific personnel, the Committee discussed the possibility of a fellowship exchange project under this Program. The program will consist of exchanges of (1) senior scientists for short periods of time to visit laboratories and (2) post-doctorate fellows for longer periods of time to participate in research and research training. In view of the significance of this Program in relation to the health of Asia the Committee agreed to recommend that the necessary steps be taken to implement the research fellowship exchange project. It was confirmed that each government would be responsible for financing the costs of its own exchange personnel.

The Committee is of the view that since W.H.O. is concerned with important medical problems in the Asian region, W.H.O. scientific staff be invited as observers to Panel meetings and conferences when the Panel in question deems it desirable. The Committee reaffirmed its intention to maintain close communication with W.H.O. representatives of the U.S. and Japanese Governments.

The Committee noted the participation of scientists from third countries in the TB-Leprosy and Parasitic Diseases conferences and agreed to invite further participation by highly qualified scientists from such countries in research and research conferences of the U.S.-Japan Cooperative Medical Science Program.

Progress of the program

During the past years the six U.S. panels have followed-up their initial programming conference in Honolulu with separate meetings to discuss and formalize the major areas of their respective disease to be attached. The priorities can be summarized as follows:

Cholera.—The panel has identified as a primary concern the unnecessarily high fatality rate in patients affected by the disease. This emphasizes the need for increased investigation of the mechanism of action of the toxins identified and their further chemical and immunologic characterization. The ultimate goal stemming from these considerations is that of developing an effective vaccine which will confer long-term immunity.

Tuberculosis.—The Tuberculosis Panel recognizes that the principal problem at this time is immunology. The relationship of hypersensitivity to protective immunity and the antigenic factors involved remains unsolved. The principal thrust of the panel then is concerned with the immunochemical and immunologic aspects of tuberculosis. Studies on hypersensitivity, characterization of antigens, and studies on the response to antigens, such as BCG, in the laboratory and in the field are the principal targets.

Leprosy.—The Leprosy Panel has singled out many of the same scientific problems that are faced by the Tuberculosis Panel. A principal problem is cultivation of M. leprae bacillus free of contaminating protein as well as being antigenically clean. Animal transmission and drug studies are also under considera-

tion. The lepra reaction and its immunologic and immunochemical base are yet unsolved. Vaccination has great potential but laboratory and field studies with protective antigens, such as BCG, must be undertaken.

Virus diseases.—The joint deliberations of the Virus Panel reached the consensus that arthropod-borne viruses and respiratory viruses should be their focus of concern. Rabies and Smallpox are also prime targets for the panel.

Parasitic diseases.—The Parasitic Diseases Panel has focused upon the problem of schistosomiasis and filariasis. They have identified problems of physiologic and biochemical characterization of the organisms as being of highest priority. They relate to the problem of immuno-diagnostic tests which are required for adequate evaluation of functional immunity, determination of drug effectiveness, and sound field or ecological studies.

Malnutrition.—The problem of malnutrition is so complex that the Malnutrition Panel has relatively broad research objectives. A primary need is seen for developing new sources of protein of adequate biologic value. This need is focused in genetic research designed to improve the amino acid distribution in cereal grains, as for example improving lysine content of rice. The interrelationship of nutrition to infection and growth and development are revealed as a high priority area. Natural toxins occurring in legumes and other plant foods as well as nutritional anemias are of great concern to the panel.

Besides delineating the priority target areas, the United States panels have met to discuss how best to implement their research program. The Secretariat, with help from the panels, has been active in three major areas:

Research grants

The panels' discussions have led to the stimulation of over one hundred research grant applications which have been reviewed by Special Study Sections composed of panel members and additional *ad hoc* consultants. The grants recommended for approval have been reviewed by an Institute Council and these applications are being processed for payment. Unsolicited grants relevant to the Program have been assigned by the Institutes to the U.S.-Japan Cooperative Medical Science Program.

Research contracts

The panels have also programmed special contract proposals to provide services or supplies of research materials and special surveys. Twelve contract proposals have been stimulated and reviewed and await negotiation. Four additional areas for contracts are being actively investigated.

Research conferences and workshops

The United States panels have held joint conferences with their Japanese counterparts and invited participants as well as holding special workshops for the American scientists active in the panel's area. These conferences and workshops have been held to stimulate and revive interest in the special areas of the U.S.-Japan Program, to communicate research results, methods and research protocol, and to plan new approaches to help solve the problems that exist in the diseases under study. The list of conferences and workshops follows:

Date	Conference title	Sponsonring panel
May 17-20, 1966	Tuberculosis and Leprosy Conference.	United States-Japan Joint Tuberculosis and Leprosy.
Aug. 15-17, 1966	Parasitic Disease Conference	United States-Japan Joint Parasitic Disease.
Aug. 20, 1966	Cholera Panel Conference	United States-Japan Joint Cholera.
Oct. 5-7, 1966	Malnutrition and Infection Conference.	U.S. Malnutrition.
Oct. 28-29, 1966	Leprosy Research Workshop	U.S. Leprosy.
Nov. 16-19, 1966	Conference on the Laboratory Evaluation of Immunization Against Tuberculosis.	U.S. Tuberculosis.

Future plans

Under the guidance of the Secretariat, the panels will hold periodic meetings to review progress of their programs and to plan their major points of thrust. The panels, with the help of the Secretariat, will continue to stimulate research grant applications and contract proposals which they feel will be relevant to the U.S.-Japan C.M.S. Program.

Future conferences and workshops are being planned to help carry out the objectives of the Program. The Malnutrition Panel will hold a joint conference with the Japanese Panel in Tokyo in February, 1967 and a conference on Low-Cost Protein-Rich Foods to be held in India in July 1967. The Cholera Panel will hold a workshop in Bethesda in January 1967 and a joint conference with the Japanese Panel will be held in San Francisco in July 1967 at the same time as a Joint Parasitic Diseases Panel Conference. The Cholera conference will stress the immunology and bacteriology of cholera, the Parasitic Diseases conference will focus on biology, physiology and immunology in the invertebrate host. The Cholera and Parasitic Diseases Conferences are being held in conjunction with the annual U.S.-Japan C.M.S. Committee Meeting.

An annual Leprosy Research Conference will be held during May 1967 in San Francisco and will focus on the use of sulfone in Leprosy. A Joint Leprosy-Tuberculosis Conference on the Biology of the Mycobacterioses is to be sponsored jointly with the New York Academy of Sciences in October 1967. The Virus Panel will be prepared to hold conferences as soon as the Japanese Virus Panel members have been appointed and they have proposed a research program.

Necessary steps are being taken to implement a fellowship program proposed and recommended at the Hakone Meeting of the U.S.-Japan C.M.S. Committee in August 1966. The program will consist of exchanges of (1) senior scientists for short periods of time to visit laboratories and (2) post-doctorate fellows for longer periods of time to participate in research and research training. Each government will be responsible for financing the costs of its own exchange of personnel.

United States-Japan Cooperative Medical Science Committee

UNITED STATES DELEGATION

Dr. Colin M. MacLeod, Chairman, Vice President for Medical Affairs, The Commonwealth Fund, 1 East 75th Street, New York, New York.

Dr. Ivan L. Bennett, Jr., Deputy Director, Office of Science and Technology, Room 200, Executive Office Building, Washington, D.C.

Dr. H. Stanley Bennett, Director, Laboratories for Cell Biology, University of Chicago, Chicago, Illinois.

Dr. Thomas Francis, Jr., Professor and Chairman, Department of Epidemiology, The University of Michigan, School of Public Health, Ann Arbor, Michigan.

Dr. James A. Shannon, Director, National Institutes of Health, Bethesda, Maryland.

Dr. James Watt, Special Assistant for Program Review, Office of the Surgeon General, Public Health Service, Room 5006 HEWS, Washington, D.C.

Dr. John M. Weir, Director of Medical and Natural Sciences, Rockefeller Foundation, 111 W. 50th Street, New York 20, New York.

Dr. Theodore E. Woodard, Professor of Medicine, University of Maryland, School of Medicine, University Hospital, Baltimore, Maryland.

JAPANESE DELEGATION

Dr. Toshio Kurokawa, Chairman, Director, Cancer Institute Hospital, Tokyo, Japan.

Dr. Hideo Fukumi, Director, Department of Bacteriology, National Institute of Health, Tokyo, Japan.

Dr. Shuji Hasegawa, President, Gunma University, Maebashi-City Japan.

Dr. Tatsuro Iwasaki, Director, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, Japan.

Dr. Kiyoshi Saito, Advisor, Institute of Public Health, Ministry of Health and Welfare, Tokyo, Japan.

Dr. Ryunosuke Nakahara, Director, Public Health Bureau, Ministry of Health and Welfare, Tokyo, Japan.

Dr. Keizo Nakamura, Director, National Institute of Health, Ministry of Health and Welfare, Tokyo, Japan.

Mr. Kiyoshi Okano, Counselor, Bureau of Higher Education and Science, Ministry of Education, Tokyo, Japan.

Mr. Eiichi Wakamatsu, Director, Bureau of Medical Affairs, Ministry of Health and Welfare, Tokyo, Japan.

Mr. Takeshi Yasukawa, Director, Bureau of North American Affairs, Ministry of Foreign Affairs, Tokyo, Japan.

Panel Members of the United States-Japan Cooperative Medical Science Program

UNITED STATES CHOLERA PANEL

Dr. Charles C. J. Carpenter, Jr., Chairman, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland 21205.

Dr. John C. Feeley, Chief, Section on Bacterial Vaccines, Division of Biologics Standards, Room 432, Building 29, National Institutes of Health, Bethesda, Maryland 20014.

Dr. Robert S. Gordon, National Institute of Arthritis and Metabolic Diseases, Room 9N222, Building 10, National Institutes of Health, Bethesda, Maryland 20014.

Dr. Willard F. Verwey, Chairman, Department of Microbiology, The University of Texas Medical Branch, Galveston, Texas.

Dr. Robert S. Oseasohn, Department of Preventive Medicine, Wearn Research Building, University Hospitals, Cleveland, Ohio 44106.

JAPANESE CHOLERA PANEL

Dr. Hideo Fukumi, Chairman, Director, Institute of Endemic Disease, Nagasaki, Japan.

Dr. Hiroshi Ogonuki, Director, Chiba Prefecture Serum Institute, Ichikawa City, Japan.

Dr. Kenji Takeya, Professor of Bacteriology, Kyushu University, Fukuoka City, Fukuoka, Japan.

Dr. Shogo Kuwabara, Professor, Faculty of Medical Science, Toho University, 774-chome Ohmori, Ohta-ku, Tokyo, Japan.

Dr. Osamu Kitamoto, Director, Institute of Infectious Diseases, Tokyo University, 1 Motofuji-cho, Bunkyo-ku, Tokyo, Japan.

UNITED STATES LEPROSY PANEL

Dr. Charles C. Shepard, Chairman, Chief, Special Projects Unit, Virology Section, Communicable Disease Center, PHS, Atlanta, Georgia 30333.

Dr. Chapman H. Binford, Medical Director, Leonard Wood Memorial, 1832 M Street, N.W., Washington, D.C. 20036.

Dr. Paul Fasal, Chief, Leprosy Service, USPHS Hospital, San Francisco, California 94118.

Dr. John H. Hanks, Johns Hopkins University, School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205.

Dr. Waldemar F. Kirchheimer, Chief, Laboratory Branch, USPHS Hospital, Carville, Louisiana 70721.

Dr. John R. Trautman, Deputy Medical Officer in Charge, USPHS Hospital, San Francisco, California 94118.

JAPANESE LEPROSY PANEL

Dr. Yoshio Yoshie, Chairman, Director, Tama National Institute of Leprosy Research, 1655, 4-chome Aoba-cho, Higashi Murayama-shi, Tokyo, Japan.

Dr. Kaoru Urabe, Department of Bacteriology, Hiroshima University, Hiroshima, Japan.

Dr. Michiaki Maeda, Research Director, Tama National Institute of Leprosy Research, 1655, 4-chome Aoba-cho, Higashi Murayama-shi, Tokyo, Japan.

U.S. PANEL ON MALNUTRITION

Dr. Nevin S. Scrimshaw, Chairman, Head, Department of Nutrition and Food Science, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139.

Dr. Robert E. Olson, Professor and Head, Department of Biochemistry, St. Louis University School of Medicine, St. Louis, Missouri 63104.

Dr. James S. Dinning, The Rockefeller Foundation, GPO Box 2453, Bangkok, Thailand.

Dr. Aaron M. Altschul, Southern Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture, 1100 Robert E. Lee Boulevard, New Orleans, Louisiana 70124.

Dr. David Coursin, 316 College Avenue, Lancaster, Pennsylvania 17603.
Dr. Henry W. Sebrell, Director, Institute of Nutritional Sciences, Columbia University, 128 Fort Washington Avenue, New York, New York 10032.

JAPANESE PANEL ON MALNUTRITION

Dr. Norio Shimazono, Chairman, Professor, Department of Biochemistry, Faculty of Medical Science, Tokyo Medical College, Tokyo, Japan.
Dr. Masao Arakawa, Professor, Department of Pediatrics, Faculty of Medical Science, Tohoku University, Sendai, Japan.
Dr. Toshio Oiso, Chief, National Institute of Nutrition, Tokyo, Japan.
Dr. Hisato Yoshimura, Professor, Department of Physiology, Kyoto Prefectural College of Medical Science, Kyoto, Japan.

U.S. PARASITIC DISEASES PANEL

Dr. Leon Jacobs, Chairman, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014.
Dr. Ernest Bueding, Professor of Pathobiology, Johns Hopkins University, 615 North Wolfe Street, Baltimore, Maryland.
Dr. Paul C. Beaver, Tulane University, 1430 Tulane Avenue, New Orleans, Louisiana.
Dr. Paul P. Weinstein, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014.
Dr. Jose Oliver-Gonzalez, Professor of Parasitology, The University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

JAPANESE PARASITIC DISEASES PANEL

Dr. Kooyo Okabe, Professor, Faculty of Medical Science, Kurume University, 67 Asahi-machi, Kurume-shi, Kurume, Japan.
Dr. Muneo Yokogawa, Professor, Faculty of Medical Science, Chiba University, 785 Yahagi-cho, Chiba, Japan.
Dr. Manabu Sasa, Professor, Institute of Infections Diseases, University of Tokyo, 1 Motofuji-cho, Bunkyo-ku, Tokyo, Japan.

U.S. TUBERCULOSIS PANEL

Dr. Gardner Middlebrook, Chairman, Institute of International Medicine, University of Maryland School of Medicine, 660 West Redwood Street, Baltimore, Maryland 21201.
Dr. William Barclay, Billings Hospital, University of Chicago, Chicago, Illinois.
Dr. Dieter Koch-Weser, Department of Demography and Human Ecology, Harvard University, School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.
Dr. Edgar E. Ribi, Molecular Biology Section, Rocky Mountain Laboratory, Hamilton, Montana.
Dr. Donald W. Smith, Department of Microbiology, University of Wisconsin, Madison, Wisconsin.

JAPANESE TUBERCULOSIS PANEL

Dr. Tatsuro Iwasaki, Chairman, Director, Research Institute of Tuberculosis, Anti-Tuberculosis Association, Kiyose-machi, Kitatama-gun, Tokyo, Japan.
Dr. Toyoho Murohashi, Director, Department of Tuberculosis, National Institute of Health, Tokyo, Japan.
Dr. Mitsuo Hori, Professor, Institute of Microbiology, Osaka University, 36 Joan-cho Kitaku, Osaka, Japan.
Dr. Yuuichi Yamamura, Professor, Faculty of Medical Science, Osaka University, 36 Joan-cho Kitaku, Osaka, Japan.

U.S. PANEL ON VIRUS DISEASES

Dr. Edwin H. Lennette, Chairman, Chief, Viral and Rickettsial Disease Laboratory, State Department of Public Health, Berkeley 4, California.
Dr. Karl Habel, Chief, Laboratory of Biology of Viruses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014.

Dr. William McD. Hammon, Head, Department of Epidemiology and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15213.
Dr. Wilbur G. Downs, Associate Director, The Rockefeller Foundation, 111 West 50th Street, New York 20, New York.
Dr. Morris Schaeffer, Director, Bureau of Laboratories, Public Health Research Institute of the City of New York, Foot of East 16th Street, New York, New York 10009.

ANIMAL RESOURCES AND PRIMATE CENTERS

Mr. NATCHER. For animal resources and primate centers you have an increase of $2 million and $1,500,000.

Describe these briefly, Dr. Shannon, and tell us why they are important and why you need the increase in funds.

Dr. SHANNON. Yes, I would be glad to. But I think technically Dr. Kennedy, who is responsible for that program, would be better.

Mr. NATCHER. Dr. Kennedy.

Dr. KENNEDY. Let me start out with a discussion of the primate center program. The program began in 1959 with the authorization of construction of seven primate centers, one of which is a national center located at Davis, Calif., and the others are regional centers.

At the present time the construction stage is over but it has actually been a phased program. The construction of the first center was completed in 1964, the last in 1966. The operations have begun in those centers that are completed.

We are requesting $1.5 million to bring the activities in the seven centers up to full capacity. At the moment, we have vacant laboratory space in these and we do not have money enough to support the complete utilization of the centers that have already been constructed. So that this $1.5 million will be used to pay supplemental applications, approved by the council, to bring the seven existing centers towards full utilization of the existing facilities.

Dr. SHANNON. That is correct, but I would like to add one thing. The care of primates is very expensive.

It would not be profitable for us to try to provide the animal resources to give every major research institution access to such experimental material. The basic decision was made, some 7 years ago, to establish, on a regional base, very adequate resources that would satisfy much more than the immediate needs of the universities where they are located so that guest investigators could be accepted for such periods of time as they needed to do work that had to be done on primates. The remainder of their work would be done in their own home laboratories. These centers are truly national resources that are distributed on a regional basis.

Mr. NATCHER. Go right ahead.

UPGRADING IN EXISTING INSTITUTIONS

Dr. KENNEDY. The $2 million increase from our present base for the other animal resource program is largely to be directed at the upgrading of the animal resources and facilities in existing institutions, an objective made urgent by the passage by the Congress last year of the act to control the transportation, sale, and handling of animals intended for use in research.

In addition to this, we will continue to support research projects directed at learning more about the diseases of laboratory animals and the natural history of the laboratory animals. Knowledge in these areas is extremely important lest there be misinterpretation of the results of experimental work. And finally, we will continue to expand the number and variety of the special colonies of animals that are particularly appropriate for certain types of research, as well as to maintain colonies of mutant strains of animals that are excellent models for human disease.

COST EFFECT OF LAW ON ANIMAL SALE, DISPOSAL, AND HANDLING

Mr. NATCHER. As you will recall, last year Congress enacted new legislation concerning sale, disposal, and the handling of animals. Has this brought about an increase as far as cost is concerned, this new legislation?

Dr. KENNEDY. I am not sure that I am the best man to speak to this, Mr. Natcher, but it is my understanding that this enactment has increased the cost of handling the animals on the part of the dealers and their unit costs have to be passed on to the consumers. Thus the costs for laboratory animals has increased as a result of this law.

Dr. SHANNON. I might add something to that. There is no doubt, and I have had enough individual contacts to know, that in some areas of the country the cost of dogs for medical research has more than doubled. In other areas they have become difficult to obtain at any price. But the story is not in at the present time.

When the Congress enacted the animal care legislation, it assigned the responsibility to the Department of Agriculture and made available to Agriculture, for the total conduct of the program, a sum of approximately $300,000. I am told that the Department of Agriculture finds it impossible to operate effectively to enforce the law with this sum and I believe that they are approaching the Congress, through their normal channels, for a substantial increase.

It will be difficult for us to know what the total impact on animal cost will be until the controls that are placed in the hands of the Department of Agriculture really become operational. I do not think the total costs will be clear to us until sometime next fall. I say this because I think it would not be profitable for us to attempt an extensive survey at this time because the situation is changing rapidly and it is not known what the Department of Agriculture will do to implement this legislation.

AUTOMATION

Mr. NATCHER. In our report last year, Dr. Shannon, as you will recall, we prodded you just a little regarding research and development in the area of automation of such patient care activities as drug orders, pharmacy records, and central medical records and certain other matters.

What are you doing and what are your plans?

Dr. SHANNON. Mr. Natcher, we are doing three things in that regard: (1) We have a very extensive, quite advanced study on the automation of clinical laboratory procedures within the clinical center that is aimed at the development of a computer-based system.

This is well on its way. It has been in process for the past 4 years, but with additional funds that were made available last year and the year before, this is developing very rapidly. It was possible, as a result of funds made available to us, to move into the area of progressive automation of the hospital as a total enterprise.

This is the responsibility of Dr. Pratt's division. The primary problem here, to be perfectly frank, Mr. Natcher, is one of cost. I think it is clearly apparent to most of us that these programs would be looked at by a person not conversant with the problem as cost-reduction programs.

They will not produce cost reductions. On the other hand, they will produce a very great increase in the capability of the hospital. Their payoff will really come when you begin to create systems of hospitals and resources that will have at their disposal centralized computer facilities.

The second thing we are doing is to study presently ongoing computer-based business-type operations in many private hospitals to see what central services can be provided. We are studying our own operation and hope to establish patterns that can be used by other hospitals.

The third activity is that we are now, for the first time, in a position to evaluate an experimental setup that was established about 4 or 5 years ago in Massachusetts General Hospital in association with Bolt, Boronek & Newman, Inc. They have established the specifications of the central hardware, the necessary computer programs, and remote access units so that the major clinical components of the hospital can store and retrieve information.

This is the first operational computer-based hospital information system in this country.

A fortunate thing has happened. On the basis of work to date, General Electric, IBM, Western Electric, and a number of other large corporate bodies are seriously looking into the feasibility of providing computer-based service to hospitals—almost on a public utility basis. Hospitals would get this service on a fee-per-transaction basis.

Now, if this develops as one expects it will, on the lines of the regional hospital system that already exists in the Rochester, N.Y., area, one will get the advantages of a centralized computer utility in very complex clinical situations. I think this is where the payoff will be, not in the individual hospital so much as in the larger hospital systems that will evolve. I think we are well on our way, but this is still going to be a fairly long haul.

Summary of Budget Request for Construction of Health Research Facilities

Mr. Natcher. Now we want to take up next Grants for Construction of Health Research Facilities.

The amount of the appropriation for 1967 I believe is $56 million and the request for 1968 is $35 million, a reduction of $21 million. But I notice, Dr. Shannon, that the justifications indicate $15 million of the 1967 appropriation will not be used until 1968.

Is that still your present estimate? I believe you did explain this from the chart.

Dr. Shannon. Yes, sir; we were directed not to commit that money for expenditure this year. So this will be available for obligation in fiscal 1968.

Mr. NATCHER. All right.

Another factor that enters into this comparison is that $6 million of the 1967 appropriation was for mental retardation centers.

Dr. SHANNON. That was the terminal year of the limited authority for special matching funds for a small number of centers for human development with special emphasis on mental retardation. That authority ends this fiscal year.

Mr. NATCHER. Ends June 30?

Dr. SHANNON. Yes, sir.

Mr. NATCHER. And you have no request for 1968 pending at this time?

Dr. SHANNON. We have not, sir.

Mr. NATCHER. So with these adjustments your obligation budget for 1968 is $50 million for health research facilities, which in round figures is $15 million more than 1967? I believe that is correct, is it not?

Dr. SHANNON. That is correct.

DEMAND FOR HEALTH RESEARCH FACILITY FUNDS

Mr. NATCHER. There is not the slightest doubt that legitimate demand far exceeds the funds you are requesting; would you agree with that, Dr. Shannon?

Dr. SHANNON. That is correct. So much so, Mr. Natcher, that we have encouraged the many institutions who inquire of us not to submit grant applications because the number of approved grants—the ones that have already been processed that will be approved—is so far in excess of the funds available that this is a useless procedure for them to go through.

Mr. NATCHER. Dr. Shannon, can you give us additional facts and figures that would illustrate this point?

Dr. SHANNON. I think Dr. Kennedy has those facts.

AUTHORIZATION COMPARED TO APPROPRIATION REQUEST

Mr. NATCHER. Dr. Kennedy, can you give us some, please; also tell us, if you will, how much your request is under the total authorization?

Dr. KENNEDY. The total authorization for 3 years—that includes fiscal years 1967, 1968 and 1969—is $280 million. The obligational authority of which we will have availed ourselves, provided this year's Presidential request is honored, will represent $85 million of the $280 million, leaving a residual of $195 million for the final year of the authorization.

Mr. NATCHER. All right. Give us some facts and figures, if you will, to illustrate the point that I just discussed with Dr. Shannon.

Dr. KENNEDY. Mr. Natcher, I suppose the best material I could give you to illustrate this point would be our present fiscal status. We have essentially obligated all the money authorized for fiscal year 1967. When that has been exhausted we will have a backlog of Council-approved and unfunded applications whose cumulative value is about $49 million. We expect, as a result of the June Council's actions on presently pending applications to add approximately $24 million more to this backlog. There is actually $40 million worth of applications pending and we expect roughly a 60-percent approval rate, if past

experience holds. So that we will close this fiscal year with a backlog of approved but unfunded applications of roughly $73 million.

I suspect that it is legitimate to project that approximately another $65 million worth of approved applications will be submitted next year, raising the total to about $140 million toward which the requested obligational authority will be applied.

Dr. SHANNON. You see, it is this disproportion between the funds that are in the request and this tremendous backlog that makes us feel that we must encourage the schools just not to submit more applications. There is no point in their expending substantial funds for planning purposes if the opportunity to obtain Federal matching is so poor.

I would only supplement or complement one thing that Dr. Kennedy said; that is, if in any budget year there is an indication that there would be a substantial relaxation in the ceiling of funds available, then I think we would obviously indicate to the schools that the opportunity for support is there.

We know from past experience that the flood of meritorious requests that would come in would really be substantial. Even in the best of years there has always been a very substantial backlog of meritorious requests.

The problem that the schools face in trying to use their own funds to take care of increased enrollments—this is both private and State universities—makes funds for capital improvements of this sort very hard to come by unless they can have some assurance of some help. I think that the figures that Dr. Kennedy used are the best evidence we have of the difference between capability and availability of funds.

Mr. NATCHER. Do you have any special problems at this time, Dr. Kennedy?

GENERAL CLINICAL RESEARCH CENTER PROGRAM

Dr. KENNEDY. The one response I would like to make to your initial question about the increases in the projected amounts for grants in the "general research and services" appropriation is to speak briefly to our request for an additional $1,980,000 for our general clinical research center program, Mr. Natcher. And I would like to frame this largely in the context of the very sharp rise that has taken place in recent times in the cost of hospitalization. These clinical centers essentially constitute a basic university resource. In the aggregate, we are supporting 1,130 research beds. And for each patient hospitalized for each day in those beds there is a hospitalization charge. Of the $28.5 million, roughly, that we are spending, approximately 40 percent is attributable to hospitalization reimbursement charges.

We have, in our own program, experienced a 20-percent rise in hospitalization costs in the last fiscal year. Since so large a portion of this budget is accounted for by hospitalization and since hospitalization charges are increasing so rapidly—and from all evidence available this

increase is by no means ended but will continue for some time—we would like the committee to keep this in mind as they evaluate the importance of this requested increase in the budget for this program.

Dr. SHANNON. Two other points.

Mr. NATCHER. All right.

Dr. SHANNON. Dr. Kennedy underestimates the hospital costs. What should be emphasized is that in addition to the 40 percent for reimbursable hospitalization, the grant includes salaries of nurses and other paramedical personnel which are increasing quite spectacularly at the present time. It will be further complicated by the application of new minimum wage laws to hospital personnel in general. To say that the 40 percent is the only item affected here is an underestimate of the case.

The second point I would make is that this is the core program in the National Institutes of Health that catalyzes the application of knowledge acquired in the laboratories to the situation of disease observed in man. I do not like to say that any single program is the most important—but I can find no other program that would be more important than this particular one at this particular point in time.

SUMMARY OF BUDGET REQUESTS FOR GENERAL RESEARCH SUPPORT GRANTS

Mr. NATCHER. Now, gentlemen, let's take up next "General research support grants," where you are requesting authority to use $61,700,000 of your 1968 appropriations for this purpose compared with $51,700,000 this year. How much of the $10 million increase is for new grants and how much is for increases in continuation grants?

Dr. KENNEDY. Well, I would have to say that the bulk of the grants in this program are not continuation grants but are 1-year grants renewed every year.

Of the total increase of $10 million, $3 million will be applied to two programs—$1.5 million will be applied to our traditional general research support grant program which has been running since 1962, and $1.5 million will be applied to the biomedical sciences support which has been running since 1966.

The purpose of the requested increases is twofold, to increase slightly the amount of the award going to institutions in the program and to fund new institutions which have become eligible as a result of the growth in their own research programs; that is, institutions which have crossed the eligibility threshold of $100,000 that we mentioned earlier today. By far and away the bulk of the $1.5 million in each of these two programs will go into the funding of newly eligible institutions.

The remaining $7 million has been allocated entirely for new grants for this new program that is directed at the creation of new centers for excellence in research and research training.

Dr. SHANNON. Again one faces the problem here: How does one retain excellence in a program and at the same time effect a more equitable distribution of science across the Nation? As best we can judge, within the authority available to us, this is the only authority that permits us to take a relatively small amount of money and, in planning with the school, really build institutions. I am not talking about building institutions in terms of building educational capability but rather to build into the institution an adequate science base upon which the instructional process can be superimposed. In the field of medicine, which is moving so fast several schools are, quite frankly, perilously close to being inadequate. They do not provide the preparation that permits a young M.D., entering on his new professional career, to continue learning because his science base is inadequate. What we are trying to do is correct that.

Mr. NATCHER. We want to thank you and Dr. Kennedy and Dr. Pratt for the presentation of this portion of your budget for the fiscal year 1968.

JUSTIFICATION MATERIAL

General Research and Services, National Institutes of Health

Amounts available for obligation

	1967	1968
Appropriation	$68,534,000	$81,141,000
Comparative transfers within NIH accounts	−153,000	
Comparative transfer from NIAID	3,000,000	
Comparative transfer frof NIAMD	600,000	
Transfer to "Operating expenses, Public Building Services," General Services Administration	−13,000	
Total	71,968,000	81,141,000

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Office of international research	81	$11,616,000	81	$14,105,000		$2,489,000
Division of computer research and technology	89	3,767,000	104	4,675,000	+15	908,000
Engineering development	6	348,000	6	347,000		−1,000
Division of research facilities and resources	153	55,969,000	158	62,014,000	+5	6,045,000
Total obligations	329	71,700,000	349	81,141,000	+20	9,441,000
Grants:						
Research		58,625,000		66,364,000		7,739,000
General research support		(53,000)		(659,000)		(606,000)
Scientific evaluation		(325,000)		(325,000)		
International centers for medical research and training		(2,800,000)		(2,800,000)		
General clinical research centers		(28,463,000)		(30,443,000)		(1,980,000)
Special resource centers		(10,850,000)		(10,850,000)		
Animal resources		(3,100,000)		(5,100,000)		(2,000,000)
Primate centers		(9,000,000)		(10,500,000)		(1,500,000)
Fellowships		1,300,000		1,580,000		280,000
Training		250,000		318,000		68,000
Direct operations:						
Collaborative research and development	2	1,766,000	2	1,991,000		225,000
International research	71	3,326,000	71	3,372,000		46,000
Computer research and technology	89	3,767,000	104	4,675,000	+15	908,000
Training activities	10	183,000	10	187,000		4,000
Review and approval of grants	116	1,395,000	119	1,511,000	+3	116,000
Program direction	41	1,088,000	43	1,143,000	+2	55,000
Total obligations	329	71,700,000	349	81,141,000	+20	9,441,000
Unobligated balance, reserve		268,000				−268,000
Total	329	71,968,000	349	81,141,000	+20	9,173,000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
Total number of permanent positions	329	349	+20
Full-time equivalent of all other positions	16	16	
Average number of all employees	291	338	+47
11 Personnel compensation:			
Permanent positions	$2,938,000	$3,346,000	+$408,000
Positions other than permanent	176,000	193,000	+17,000
Other personnel compensation	11,000	12,000	+1,000
Total personnel compensation	3,125,000	3,551,000	+426,000
12 Personnel benefits	356,000	399,000	+43,000
21 Travel and transportation of persons	766,000	792,000	+26,000
22 Transportation of things	81,000	83,000	+2,000
23 Rent, communications, and utilities	231,000	287,000	+56,000
24 Printing and reproduction	71,000	74,000	+3,000
25 Other services	3,160,000	3,441,000	+281,000
Project contracts	1,603,000	1,816,000	+213,000
Payment to "National Institutes of Health management fund"	742,000	818,000	+76,000
26 Supplies and materials	98,000	123,000	+25,000
31 Equipment	1,292,000	1,495,000	+203,000
41 Grants, subsidies, and contributions	60,175,000	68,262,000	+8,087,000
Total obligations by object	71,700,000	81,141,000	9,441,000

Summary of changes

1967 enacted appropriation	$68,534,000
Unobligated balance, reserve	−268,000
Comparative transfers to/from other accounts	−153,000
Comparative transfer from NIAMD	+600,000
Comparative transfer from NIAID	+3,000,000
Transferred to "Operating expenses, Public Buildings Service," General Services Administration	−13,000
1967 total estimated obligations	71,700,000
1968 estimated obligations	81,141,000
Total change	+9,441,000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built-in:				
1. Annualization of new positions authorized in 1967				$158,000
B. Program:				
1. Research grants		$58,625,000		7,739,000
2. Fellowships		1,300,000		280,000
3. Training		250,000		68,000
4. Collaborative research and development	2	1,763,000		226,000
5. International research	71	3,209,000		22,000
6. Computer research and technology	89	3,646,000	15	752,000
7. Training activities	10	169,000		3,000
8. Review and approval	116	1,236,000	3	99,000
9. Program direction	41	760,000	2	35,000
C. Payment to "National Institutes of Health management fund" for centrally furnished services:				
1. Collaborative research and development		3,000		
2. International research		117,000		12,000
3. Computer research and technology		121,000		30,000
4. Training activities		14,000		1,000
5. Review and approval		159,000		17,000
6. Program direction		328,000		16,000
Total program increases			20	9,300,000
DECREASES				
A. 1 less day of pay in 1968				−17,000
Total decreases				−17,000
Total net changes requested			20	9,441,000

EXPLANATION OF CHANGES

Research grants—The increase of $7,739,000 includes $1,653,000 for regular research grants, $606,000 for general research support grants, $1,980,000 for general clinical research centers, $2,000,000 for animal resources, and $1,500,000 for primate centers.

Fellowships—$100,000 of the total increase of $280,000 will provide support for 10 existing and eight new postdoctoral fellowships for the Division of Research Facilities and Resources. This Division first began their fellowship program in 1967. The remaining $180,000 will be utilized by the Office of International Research to increase the annual stipend level and to increase the total number of their fellowships to 170.

Training grants—The increase of $68,000 will provide support for two new grants affording training to approximately 30 graduate students. This training program was new to the Division of Research Facilities and Resources in 1967.

Collaborative research and development—The increase of $226,000 provides support for further development of the Pharmacology-Toxicology information program and includes a small amount ($35,000) for contracts for special research resources.

International research—The increase of $22,000 will provide funds for increased operating costs.

Computer research and technology—The increase of $752,000 and 15 positions will provide: additional depth and technical support in biological, physical and behavioral sciences as they relate to the mathematics and statistics of computer technology, for research in pattern recognition through the use of optical scanning devices, and for development of a natural language processing system.

Training activities—The $3,000 increase provides for increased operational costs.

Review and approval—The increase of $99,000 and three positions are needed for the administration of the several grant programs, and for the processing and fiscal management of grants.

Program direction—The increase of $35,000 and two positions will provide additional staff required for over-all administration, planning and evaluation.

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".

Explanation of transfers

	1967 estimate	Purpose
Transfer to: "Operating expenses. Public Buildings Service," General Services Administration.	−$13,000	Transfer of rental costs to GSA.
Comparative transfer to: Other NIH accounts	−153,000	Redistribution of the National Institutes of Health management fund.
Comparative transfer from:		
NIAMD	+600,000	For the United States-Japan program.
NIAID	+3,000,000	

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

ITEM	ACTION TAKEN OR TO BE TAKEN
1967 Senate Report	
(1) The Committee directed the Division of Research Facilities and Resources to devote some of the funds provided for the General Clinical Research Center program to establish, on an experimental basis, a limited number of outpatient clinical research centers in connection with well-established outpatient clinics serving an adequate number of patients with chronic diseases to warrant an investment in the necessary research facilities and research staff.	(1) Outpatient clinical research centers will be established within the limitations on availability of funds.
1967 House Report	
(1) Committee was "anxious that the Division of Computer Research and Technology should proceed as rapidly as possible with the automation of such patient care activities as drug orders and pharmacy records, admissions, and medical records, and the installation of remote computer systems capable of drawing on the central Division facility."	(1) Research and development in the Clinical Center automation project has continued during fiscal year 1967 and an extensive systems analysis for inventory control has been conducted in the pharmacy and will be implemented this year. Initial systems analysis is being done on the out-patient and medical record functions. Six automated chemical tests (Auto Analyzer) have performed successfully on-line for four months and an Enzyme Assay System and Remote Hemotology Entry System will soon be integrated into daily service. Two contracts have been awarded to establish remote computer capabilities for use by certain NIH scientist and DCRT personnel to gain experience with this mode of computing by using actual problems. This experience will be invaluable in evaluating the most productive remote computer services that should be provided at NIH.

OFFICE OF INTERNATIONAL RESEARCH

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research	--------	$6,907,000	--------	$9,166,000	--------	+$2,259,000
International centers for medical research and training	--------	(2,800,000)	--------	(2,800,000)	--------	----------
Fellowships (international postdoctoral)	--------	1,200,000	--------	1,380,000	--------	+180,000
Direct operations:						
International research	71	3,326,000	71	3,372,000	0	+46,000
Training activities	10	183,000	10	187,000	0	+4,000
Total obligations	81	11,616,000	81	14,105,000	0	+2,489,000

Research grants

	1967 estimate	1968 estimate	Increase or decrease
Regular projects	$4,034,000	$5,687,000	+$1,653,000
Special program	2,873,000	3,479,000	+606,000
Total research grants	6,907,000	9,166,000	+2,259,000
Research project grants to former international postdoctoral fellows	434,000	587,000	+153,000

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 subprofessional technical assistance, equipment and supplies, and serve not only to protect the training investment made in the foreign scientist by encouraging the inauguration 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 1967 AND 1968

This Program and its closely related foreign fellowship program are useful and important devices for building and improving scientific communication between the United States biomedical science community and its counterparts in other countries. In 1967, 154 awards will be made for a total $454,000. The 1968 estimate will support 215 awards for 587,000.

Research project grants (United States-Japan program):	
1967 estimate	$3,600,000
1968 estimate	5,100,000
Increase or decrease	+1,500,000

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 October 4–7, 1965 and subsequently in Hakone, Japan during August 17–19, 1966.

The program is concerned with the diseases of mutual importance to the health of the people 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 secretaries. 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 PL 86–610, provides for the support of scientific projects, is responsibile 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 C.M.S. Program, and provides and funds the U.S. scretariat.

PROGRAM PLANS IN 1967 AND 1968

The allowance of $3,600,000 for grants in 1967 will provide for approximately 113 research grants in the areas of cholera, leprosy, tuberculosis, virus diseases, infectious diseases and malnutrition. The requested amount of $5,100,000 in 1968 will be provide for the continuation of these 113 research grants started in 1967 and the provision for about 89 new research project grants.

The increase in total regular research grants resulting largely from the transfer of the U.S.-Japan program to OIR leads to the increase of $606,000 for the general research support grants program.

International centers for medical research and training:	
1967 estimate	$2,800,000
1968 estimate	2,800,000
Increase (+) or decrease (—)	----------

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:

U.S. University	*Foreign affiliate institution*
Johns Hopkins University	All India Institute of Hygiene and Public Health and the Calcutta School of Tropical Medicine, Calcutta, India.
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 1967 AND 1968

Further efforts to broaden the research base of the existing ICMRT's are underway. Program Directors have been encouraged to broaden their programs whenever possible through additional health-related research projects mounted upon the 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 post-reviews that these ICMRT organizations are now providing unexcelled research and training opportunities for American scientists which cannot be duplicated in the United States.

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations: (a) Noncompeting	79	$192,000	247	$3,936,000	+168	$3,744,000
2. New	188	3,842,000	170	1,751,000	−18	−2,091,000
3. Subtotal, regular program	267	4,034,000	417	5,687,000	+150	+1,653,000
4. General research support grants		53,000		659,000		+606,000
5. Scientific evaluation		20,000		20,000		
6. ICMRT		2,800,000		2,800,000		
7. Total, research grants		6,907,000		9,166,000		+2,259,000

Fellowships

	1967 estimate	1968 estimate	Increase or decrease
Fellowships (international postdoctoral)	$1,200,000	$1,380,000	+$180,000

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 1967 AND 1968

This program will be continued in the 43 countries that participated in 1966. 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 when he is at the peak of his effectiveness. In order to provide for increased living costs, it is expected that authorization to increase the stipend levels of domestic fellows will be made during 1967. The additional funds requested for this program in 1968 will allow an increase of $1,000 in the stipend level from $6,000 to $7,000 per year, thus making the international fellows stipends equal to that of domestic fellows.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
Continuations	65	$314,000	70	$355,000	+5	+$41,000
New grants	101	886,000	100	1,025,000	−1	+139,000
Total fellowships	166	1,200,000	170	1,380,000	+4	+180,000

International research

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	71	$904,000	71	$938,000		+$34,000
Other expenses		2,422,000		2,434,000		+12,000
Total	71	3,326,000	71	3,372,000		+46,000

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 1967 AND 1968

In 1967 and 1968 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 evaluates, 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 as it affects grants which are made to scientists located abroad.

The request also provides for staff to operate and coordinate the NIH program utilizing U.S. owned foreign currency (P.L. 480 program).

Support is also provided for an analytic activity which advises NIH management on the extent, scope, direction and relevance of NIH grants abroad. This activity collates information on medical research efforts of other countries to show the mutual effects of these efforts with those of NIH.

In addition to the above programs, the Office of International Research operates a new cooperative venture entitled the U.S.-Japan Cooperative Medical Science Program. The primary areas in this program are: cholera, leprosy, tuberculosis, parasitic diseases, virus diseases and nutrition. The request provides for funds for conferences between United States and Japanese scientists and support of scientific studies by contract.

The increase of $46,000 which is requested includes $22,000 for increased operating costs, $15,000 for annualizations of positions new in 1967, an offset of $3,000 for one less day of pay in 1968 and an increase of $12,000 for centrally furnished services from the "National Institutes of Health Management Fund."

TRAINING ACTIVITIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	10	$120,000	10	$123,000	--------	+$3,000
Other expenses	--------	63,000	--------	64,000	--------	+1,000
Total	10	183,000	10	187,000	--------	+4,000

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 1967 AND 1968

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. The additional $4,000 requested in 1968 provides $3,000 for increased operating costs and an increase of $1,000 for centrally furnished services from the "National Institutes of Health Management Fund".

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	89	$842,000	104	$1,170,000	+15	+$328,000
Other expenses	--------	2,925,000	--------	3,505,000	--------	+580,000
Total	89	3,767,000	104	4,675,000	+15	+908,000

INTRODUCTION

The Division of Computer Research and Technology plans and conducts research, developmental, and demonstration programs in mathematical and other computer related sciences in support of NIH programs; provides a professional and technical advisory resource in all relevant areas of mathematics and other computer-related sciences; formulates and administers NIH-wide policies, standards, methods, and procedures regarding computation and data processing activities; and plans and conducts appropriate training of the National Institutes of Health staff.

PROGRAM PLANS IN 1967 AND 1968

With the appointment of its first Director in 1967, the Division is concentrating on building a top professional staff and in clarifying and redefining organizational functions and relationships. The major effort during 1967 is focused on an extensive program to develop a computer technology adequate to support the biomedical research and administrative activities of the National Institutes of Health. This undertaking will continue through 1968 and is designed to produce a technology capable of realizing the full potentialities of the newly acquired IBM 360 computing system. Toward the accomplishment of this goal the Division will: 1) acquire the necessary general and special-purpose computer hardware and begin to develop the supporting software, tools and computer languages; 2) develop a responsive interactive computer technology which will be made available to the laboratory scientists and management staff of NIH through the use of remote stations and, 3) develop the technology required to couple laboratory data-generating equipment with the more powerful processing capability of a large central computer.

During 1968 the Division, which will be in its third year of development, is requesting an increase of 15 new positions and a net increase of $908,000. The new positions are required to provide depth and technical support in biological, physical, and behavioral sciences as they relate to the mathematics and statistics of computer technology. In addition to the $202,000 needed in support of the requested new positions, there are three major areas of future program development planned as follows: 1) a major expenditure of $300,000 will be used to explore the ways in which computers coupled with optical scanning devices can aid the scientist by recording, classifying, storing and retrieving large volumes of data. Equipment will be designed to interpret data from X-rays and microphotographs and automatically scan additional specimens; 2) an additional $200,000 is requested to pursue the development of a natural processing system whereby a scientist using a predetermined vocabulary of English language words can communicate with the computer without having to rely on intermediary programming and the accompanying and resulting delays in reading the problem at hand; and 3) an increase of $50,000 is requested to establish a broad training program at the NIH whereby the scientists and administrators can effectively use the power and speed of modern computer technology in their programs. Included in the requested net increase is $126,000 for mandatory items usch as annualization of positions new in 1967, partially offset by one less day of pay in 1968. There are also increases of $30,000 for centrally furnished services from the "National Institutes of Health Management Fund."

ENGINEERING DEVELOPMENT

Program direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	6	$82,000	6	$82,000		
Other expenses		266,000		265,000		−$1,000
Total	6	348,000	6	347,000		−1,000

INTRODUCTION

This activity, currently funded in total within Program Direction, began in fiscal year 1967 to plan for a centralized medical engineering development component. The efforts of this organization are to be directed towards applying engineering and technological innovations to biomedical problems. The major functions contemplated include the conduct of research and technical development; systems analysis engineering; engineering consultation, surveillance and development; and technical fabrication and services.

The request for 1968 represents a decrease of $1,000. The program amounts are the same for both years; the decrease represents a reduced amount for centrally furnished services from the National Institutes of Health Management Fund.

PROGRAM PLANS IN 1967 AND 1968

From the engineering developments and technological innovations of recent years and the opportunities that such work in other fields provided for advancing medical research and diagnostic and treatment procedures, there has evolved the concept of a distinct activity managing target research and development programs of a bioengineering nature.

NIH has had the opportunity to review the valuable work of the Wooldridge Committee which reviewed NIH planning and organization generally, and the Ruina Committee which concentrated on the organization of developmental and contract activities. NIH further consulted with external engineering resources such as M.I.T., the Aerospace Corporation and Bell Laboratories, and engaged in substantial internal review. Out of these efforts, NIH has determined that a new organizational and functional pattern must be established which will (1) consolidate the existing NIH technical elements engaged in bioengineering and technical development, (2) furnish leadership and competence for further evaluation and growth, and (3) provide for critical surveillance and review of all NIH contract activities in these fields.

It is planned that the substantive responsibility for the design and direction of directed research and development programs such as the Artificial Heart and Artificial Kidney will remain in the particular Institute which has categorical responsibility for the specific area of research. Other bioengineering elements and related functions—existing or to be developed—which would be grouped centrally include:

1. Research and technical development based on the physical sciences and applicable to the resolution of biomedical problems in the areas of materials, analytical methods and instrumentation, and clinical methods and instrumentation.
2. The development of systems analysis capability encompassing the modeling and analysis of complex biological, physical, social and managerial systems.
3. The elements necessary to provide critical surveillance and specialized engineering consultation relative to the design, instrumentation and apparatus for intramural activities and/or the directed research programs and contracts of the Institutes and Divisions.
4. The activities involved in fabrication, modification and servicing of instruments, research equipment and special purpose devices utilized in NIH's intramural research activities.

The NIH request for fiscal year 1968 constitutes a minimal figure if, as we expect, a new Division is established either late in fiscal year 1967 or early in fiscal year 1968. To the degree that this Division includes the transfer of certain functions from other NIH components (e.g., the Biomedical Instrumentation and Engineering Branch, Division of Research Services) the positions and dollars from these components will need to be transferred to the Engineering Development account.

Division of Research Facilities and Resources

Obligations by activity

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$51,718,000		$57,198,000		+$5,480,000
General clinical research centers		(28,463,000)		(30,443,000)		(+1,980,000)
Scientific evaluation		(305,000)		(305,000)		
Special research resources		(10,850,000)		(10,850,000)		
Animal resources		(3,100,000)		(5,100,000)		(+2,000,000)
Primate centers		(9,000,000)		(10,500,000)		(+1,500,000)
Fellowships		100,000		200,000		+100,000
Training		250,000		318,000		+68,000
Direct operations:						
Collaborative research and development	2	1,766,000	2	1,991,000		+225,000
Review and approval of grants	116	1,395,000	119	1,511,000	+3	+116,000
Program direction	35	740,000	37	796,000	+2	+56,000
Total obligations	153	55,969,000	158	62,014,000	+5	+6,045,000

Research grants

	1967 estimate	1968 estimate	Increase or decrease
General clinical research centers	$28,463,000	$30,443,000	+$1,980,000
Scientific evaluation	305,000	305,000	
Special research resources	10,850,000	10,850,000	
Animal resources	3,100,000	5,100,000	+2,000,000
Primate centers	9,000,000	10,500,000	+1,500,000
Total research grants	51,718,000	57,198,000	+5,480,000

INTRODUCTION

The primary mission of the Division of Research Facilities and Resources is to provide the nation's scientific community with the research resources and the research facilities essential for sustaining and advancing the national biomedical research and research training program. Its program underpins a broad spectrum of science by supporting services that are useful across the total panorama of biomedical research. The Division administers programs which provide support: for clinical research centers where physicians and scientists can study human diseases; 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 General Clinical Research Center program was established to provide, in both effective form and adequate numbers, the facilities and resources in which the nation's clinical investigators can study human disease and related problems in human biology. The program is designed: to increase understanding of the nature and natural history of disease; to extend the capability of medical science to treat and manage disease; to apply at the bedside the fundamental biological knowledge acquired in this basic research program; to train medical students

and young physicians in the techniques and the discipline of clinical investigation; and to conduct demonstrations of new techniques and new therapeutic procedures for the instruction of medical practitioners.

Each center is a separate unit with a full-time senior clinical investigator serving as program director, a specified number of beds, a complement of nurses and technicians, and integral laboratories and supporting facilities. Within the entire complex, scientists from many disciplines work together in the conduct of exacting clinical research. Areas of research at these centers include aging, blindness, cancer, cardiovascular disease, and diseases contributing to infant mortality, cerebral vascular disease, neuropsychiatric disorders, transplantation of organs, and diseases of metabolism, especially diabetes mellitus.

As of June 30, 1966 awards have been made to fund 89 centers.

PROGRAM PLANS IN 1967 AND 1968

The $28,463,000 available in 1967 to the General Clinical Research Center program will provide support to the existing centers and fund approximately three new centers. It is anticipated that by the close of 1967 that approximately 92 center awards will have been made. The $30,443,000 requested for 1968 will provide continuing support for the existing centers and within the limitations on availability of funds, will establish a limited number of outpatient centers as directed by the Report of the Senate Appropriations Committee, submitted in connection with the DHEW Appropriations for 1967.

Although the General Clinical Research Center program has provided many institutions with excellent facilities for the study of the hospitalized patient, the current outpatient facilities are grossly inadequate to meet the requirements for controlled clinical experimentation. Qualified experts have estimated that the major portion of human disease—as high as 90–95 percent—occurs in ambulatory patients. Therefore, just as inpatient clinical research centers have provided an environment which is far superior to the open ward, so will the special outpatient research centers, removed from the overburdened hospital outpatient service departments, provide in analogous fashion another urgently needed type of resource for clinical investigation.

The following are a few of the many projects conducted in General Clinical Research Centers during the past year:

Cancer.—At the University of Vermont General Clinical Research Center a new method for detection of cancer of the cervix has been developed; the technique indicates whether a therapeutic procedure destroyed or removed all of the neoplastic tissue.

Infant mortality.—At Stanford University an alarm device in premature infants signals to staff whenever a baby has been apneic (transient cessation of respiration) for more than 30 seconds. In response to the alarm, a nurse can recognize the apnea at a stage when simple stimulation alone will restore normal breathing patterns. This will prevent brain damage and mental retardation caused by unrecognized hypoxia (lack of oxygen) due to apnea.

Strokes.—Investigators at the University of Chicago School of Medicine have developed a new approach to the problem of cranial aneurysms, a major cause of strokes. Thrombosis of these dangerous lesions is produced by the passage of direct current across the aneurysm by means of a stainless steel electrode introduced by stereotaxic insertion.

Scientific evaluation

The $305,000 requested for 1968 will support the study sections and 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 forward their recommendations to the appropriate National Advisory Council.

Special research resources

This program provides support to enhance the research capability of the nation through application of large-scale equipment and instrument-oriented resources to areas of major multidisciplinary research endeavor. These special resources include computing centers for medical and biological materials production and for scientific and technical information. Since such resources are usually too costly to be assigned to a single investigator, they are established for use by a community of scientists on an institutional, regional (city, state, section), or national basis.

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 are growing rapidly as the sophistication, capabilities, and costs of modern research increase. The progressive quantification of the biological sciences is reflected in the increasing requirements for specialized equipment, such as computers and analytical 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 the dependence upon 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 interaction 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.

This program has been in existence since July 1962. At the present time support is being provided for 59 centralized resources of which 43 are computer centers, six analytical biochemistry instrumentation, three biological materials, three information sciences, and four biological instrumentation resources. Support will be provided for another computer center which will be activated in 1967.

PROGRAM PLANS IN 1967 AND 1968

The $10,850,000 available in 1967 and an equal amount requested in 1968 will provide continuing support of the existing facilities.

Animal resources

Any innovation—from a life-saving therapeutic procedure to a simple physiological manipulation—cannot be undertaken in man until exhaustively tested in the experimental animal. The rapid growth of biomedical research has imposed a substantial requirement for laboratory animal resources that will provide animals of the quality and in the quantity needed by all branches of specialized research. In addition, certain species of animals are becoming increasingly important for the development of model systems and systematic efforts will have to be made to provide such animals in adequate numbers and properly conditioned for experimental use.

Of primary importance is a program of project grants in the special field of laboratory medicine to provide important data and information concerning the major laboratory 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. Such information

provides essential background information to the research worker and also provides the basis for improved standards of animal care.

Projects to define and develop new and useful animal biological models for medical research and studies to establish physiological and behavioral base lines on animal strains and species for which information is not now available warrant high priority. Special studies in genetics of laboratory animals must be undertaken to develop and maintain strains with anatomical, physiological, or biochemical variants in order to accelerate progress in major areas such as metabolic diseases, muscular dystrophy, and cancer.

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 endeavors and the growing national concern that research animals be given optimal care at all times, made it imperative that all institutions engaged in medical research provide adequate care for research animals. Grants should be made to assist in the initiation of such programs by providing funds for necessary alterations and renovations, for the salaries of key personnel, and for specialized equipment such as animal surgery equipment, anesthesia machines and cage washing facilities. Diagnostic laboratories to assist in the early detection of animal diseases and identification of inapparent infections so disastrous to research studies are essential components of a sound institutional animal resources program.

PROGRAM PLANS IN 1967 AND 1968

The $3,100,000 available in 1967 will provide support for 26 ongoing resources and the establishment of 15 new resources.

New needs resulting from: toxicology studies, heart disease research, leukemia studies, chemotherapy research for the control and treatment of infectious diseases, development of vaccines, and other significant studies are placing greater demands on institutional animal resources.

The passage of PL 89-544, dated August 24, 1966 which provides that certain animals intended for use in research facilities be provided humane care and treatment will require renovation of a large number of institutional facilities to meet the new standards. The $5,100,000 requested for 1968, an increase of $2,000,000 would provide support for 41 ongoing, and an estimated 10 new grants for animal resources including renovation of institutional facilities to meet the new standards.

Primate centers

Essential in the development of knowledge for the prevention and control of disease in man is the ability to gain an understanding of basic physiological and biochemical processes through experimentation on living systems. Since extrapolation from studies with lower animals directly to man is of limited validity and because nonhuman primates are afflicted with diseases similar to those of man, research on primates in many respects, is invaluable as a prelude to clinical investigation in man.

The Primate Centers program was established by the 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 best be studied by utilizing the subhuman primate as the biological model.

PROGRAM PLANS IN 1967 AND 1968

Construction of the six regional centers and one national center have now been completed and all have ongoing research programs which are developing as rapidly as available funds will allow. Significant accomplishments have al-

ready been realized in infectious disease studies, reproduction and population control, and mental retardation to name only a few. Of equal importance is the rapidity with which information on the colonization, breeding and maintenance of the primate 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.

As with any developing program there exists a continuing need for increasing support. Construction of all centers has recently been completed and ongoing research programs will now develop more rapidly. The projected estimates, as reflected in the funding for 1967 and 1968 are based on space and facilities now available for occupancy, scientific staff requirements and increasing costs of center operations as the various centers approach a stable level of full activity.

Plans in 1967 and 1968 provide for continuation of support of all seven primate centers as follows:

	1967 estimate	1968 estimate
Regional primate research centers:		
1. Medical Research Foundation of Oregon, Portland, Oreg	$1,700,000	$2,100,000
2. University of Washington, Seattle, Wash	1,265,000	1,500,000
3. University of Wisconsin, Madison, Wis	1,450,000	1,500,000
4. Emory University, Atlanta, Ga	1,175,000	1,500,000
5. Tulane University, New Orleans, La	1,340,000	1,400,000
6. Harvard University, Boston, Mass	1,000,000	1,300,000
National Center for Primate Biology:		
7. University of California, Davis, Calif	1,070,000	1,200,000
Total	9,000,000	10,500,000

Fellowships

Total fellowships:	
1967 estimate	$100,000
1968 estimate	200,000
Increase or decrease	+100,000

INTRODUCTION

Increased numbers of specialized research personnel are required for the conduct of expanded research programs in laboratory animal science and medicine. At present, there are inadequate numbers of such highly trained individuals. Scientists with demonstrated ability in the laboratory-animal sciences will be encouraged to accept fellowships awarded to pursue special problems in experimental anesthesiology, pathology, virology, primatology, biochemistry, etc., in order to help meet these needs.

PROGRAM PLANS IN 1967 AND 1968

The $100,000 available in 1967 will provide support for ten new special fellowships at the postdoctoral level. The $200,000 requested for 1968 would provide continued support for the ten existing fellowships and eight new fellowships.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations: Noncompeting	0	0	10	$120,000	+10	+$120,000
2. New	10	$100,000	8	80,000	−2	−20,000
3. Total fellowships	10	100,000	18	200,000	+8	+100,000

Training

Total training grants:	*Amount*
1967 estimate	$250,000
1968 estimate	318,000
Increase or decrease	+68,000

INTRODUCTION

The increased use of animals in medical research programs, not only in total numbers, but also in the variety of species, and the attention being focused on the necessity of using animals raised under controlled conditions and of known "pedigree," have resulted in a great demand by medical research institutions for professional support by specialists in laboratory animal medicine. A National Academy of Sciences—National Research Council study group has estimated that approximately 1,100 veterinarians with specialty training in laboratory animal medicine are needed by research institutions whereas presently only approximately 250 are available. This problem has a serious impact on present and future medical research efforts since the task of such people is to insure the ready availability of the appropriate biological model systems with which the investigator can work to study and resolve major medical problems.

PROGRAM PLANS IN 1967 AND 1968

The $250,000 available in 1967 will provide support for seven training grants at the graduate level in the field of laboratory animal medicine. The $318,000 requested in 1968 would support the seven ongoing grants and two new grants providing training to approximately 30 graduate students.

The program will include graduate training in pathology, microbiology, surgery, physiology, genetics, and other specialized fields as they relate to laboratory animals.

Distribution of training grants

Graduate	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations: Noncompeting	7	$250,000	7	$250,000	0	0
2. New	0	0	2	68,000	+2	+$68,000
3. Total training grants	7	250,000	9	318,000	+2	+68,000

Collaborative research and development

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	2	$30,000	2	$30,000	0	0
Other expenses	.....	1,736,000	.....	1,961,000	.....	+$225,000
Total	2	1,766,000	2	1,991,000	0	+225,000

This activity supports studies carried out primarily by non-government scientists in cooperation with the scientific staff of this Division. These studies are financed through research contracts—continuing year to year commitments which are renegotiated each year.

PROGRAM PLANS IN 1967 AND 1968

It is anticipated that 13 or 14 contracts will be made in 1967 in the areas of special research resources, Pharmacology-Toxicology information and laboratory animal care.

The increase includes $191,000 for support of the Pharmacology-Toxicology information program to accelerate the development and realization of methodologies and of systems for handling numerical data and other information related to the interactions between living systems, exogenous drugs, and poisons, as well as endogenous chemical compounds. Funds will be used to provide resources for the conduct of studies ranging from exploratory research through preliminary design and testing of modern systems for making accessible to a variety of classes of scientific research workers and other users the already large and rapidly increasing body of information in this area. The remaining $35,000 will provide additional support for contracts for special research resources.

Review and approval of grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	116	$1,129,000	119	$1,200,000	+3	+$71,000
Other expenses		266,000		311,000		+45,000
Total	116	1,395,000	119	1,511,000	+3	+116,000

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 Committee, the National Advisory Council on Health Research Facilities and the National Advisory Health Council; and liaison with applicants, grantees, other components of the NIH, the PHS, advisory bodies, and interested organizations.

The increase requested will provide three positions and $99,000 for assistance in program management.

Included in the net increase is $6,000 for a mandatory increase due to annualization of positions new in 1967 offset by one less day of pay in 1968. There are also increases of $17,000 for centrally furnished services from the "National Institutes of Health management fund."

Program direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	35	$374,000	37	$407,000	+2	+$33,000
Other expenses		366,000		389,000		+23,000
Total	35	740,000	37	796,000	+2	+56,000

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 $35,000 will be used for increased operating costs and support of two positions for program administration.

Included in the net increase is $5,000 for a mandatory increase due to annualization of positions new in 1967 offset by $1,000 for one less day of pay in 1968. There is also an increase of $17,000 for centrally furnished services from the "National Institutes of Health management fund".

New positions requested in 1968

	Grade	Annual salary
DIVISION OF RESEARCH FACILITIES AND RESOURCES		
Review and approval of grants:		
Chief of branch (1)	GS-16	$20,075
Clerical assistant (1)	GS-6	5,867
Do	GS-5	5,331
Total (3)		31,273
Program direction:		
Public health program specialist (1)	GS-14	15,106
Clerical assistant (1)	GS-5	5,331
Total (2)		20,437
Subtotal—Division of Research Facilities and Resources (5)		51,710
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY		
Mathematician (2)	GS-15	35,100
Research mathematician (2)	GS-14	30,212
Engineer (1)	GS-14	15,106
Mathematician (2)	GS-13	25,746
Systems analyst (1)	GS-12	10,927
Engineer (1)	GS-12	10,927
Mathematician (1)	GS-12	10,927
Computer programmer (2)	GS-11	18,442
Do	GS-9	7,796
Secretary (2)	GS-5	10,667
Subtotal—Division of Computer Research and Technology (15)		175,750
Total new positions, all activities (20)		227,460

Grants for Construction of Health Research Facilities

Amounts available for obligation

	1967	1968
Appropriation	$56,000,000	$35,000,000
Unobligated balance brought forward	27,350	15,000,000
Unobligated balance, end of year	−15,000,000	
Total	41,027,350	50,000,000

Obligations by activities

	1967 estimate	1968 estimate	Increase or decrease
Grants for construction and equipment:			
(a) Health research facilities	$35,001,550	$50,000,000	+$14,998,45
(b) Centers for research on mental retardation	6,025,800		−6,025,800
Total obligations	41,027,350	50,000,000	+8,972,650

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
41 Grants, subsidies, and contributions (total obligations)	$41,027,350	$50,000,000	+$8,972,650

SUMMARY OF CHANGES

1967 enacted appropriation	$56,000,000
Unobligated balance brought forward	27,350
Unobligated balance end of year	−15,000,000
1967 total estimated obligations	41,027,350
1968 estimated obligations	50,000,000
Total change	8,972,650
Increases: Health research facilities	+15,000,000
Decreases:	
Health research facilities	−1,550
Centers for research on mental retardation	−6,025,800
Total decreases	−6,027,350
Total net change requested	+8,972,650

EXPLANATION OF CHANGES

The increase of $8,972,650 is a result of $15,000,000 appropriated in 1967 for Construction of Health Research Facilities which will become available in 1968, offset by $6,000,000 due to the expiration June 30, 1967 of the authorization for Construction of Centers for Research on Mental Retardation and adjusted for balances brought forward in F.Y. 1967.

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".

The 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.—

"Sec. 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."

"Sec. 704. There is hereby authorized to be appropriated for the fiscal year ending June 30, 1957, and for each of the nine suceeding fiscal years, not to exceed $50,000,000, 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."

AUTHORIZATION OF APPROPRIATIONS

"Sec. 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."

	1967 estimate	1968 estimate	Increase or decrease
Health research facilities	$50,000,000	$35,000,000	−$15,000,000
Unobligated balance brought forward	1,550	15,000,000	+14,998,450
Unobligated balance, end of year	15,000,000	0	+15,000,000
Subtotal, health reseachs facilities	35,001,550	50,000,000	+14,998,450
Centers for research on mental retardation	6,000,000	0	−6,000,000
Unobligated balance brought forward	25,800	0	−25,800
Subtotal, mental retardation	6,025,800	0	−6,025,800
Total	41,027,350	50,000,000	+8,972,650

The major objectives of the Health Research Facilities Program are to meet needs for new and replacement facilities for this Nation's research program in the health sciences, including the construction of biomedical research facilities in medical or dental schools, special centers for the study of aging, human reproduction, pharmacology and toxicology, and the construction and renovation of animal facilities. These modern facilities are essential to the Nation's colleges, universities, and non-profit research institutions in effectively prosecuting research efforts leading to better health for the American people. This program authorizes grants for up to 50 percent of the cost of the facility, to be dedicated to research in the health sciences for a minimum of ten years by the recipient institution.

For the last two decades the imbalance between the rate of manpower development and the rate of facilities construction, replacement, and renovation has steadily widened. Although this imbalance will continue to grow and to result in serious overcrowding of research space, the requested $35 million will help make it possible to meet a portion of these needs by providing approximately 1,300,000 net square feet of space to house 6,500 full-time equivalent research workers. This space will contribute to the continuing program efforts of the NIH categorical institutes and will provide research space for young scientists emerging from training programs which is essential to their commitment to research careers. The construction of health research facilities will continue to be coordinated with the goals of the several categorical institutes, thus expanding the national capability for research in cancer, metabolic diseases, arthritis, heart disease, mental illness, etc. Historically, total appropriations of $430 million have been made by Congress through 1967 for Health Research Facilities construction of which $415 million will have been obligated by the end of fiscal year 1967. Since the inception of the program, 1,832 applications have been received requesting a total of $701 million.

Upon the recommendation of the National Advisory Council on Health Research Facilities, the Surgeon General has thus far awarded 1,383 grants, totaling $395,987,714. This amount for construction is more than doubled by the non-federal matching funds contributed by the grantees.

Medical schools	$210, 494, 573
Dental schools	9, 328, 760
Schools of public health	8, 554, 724
Other health-related schools [1]	85, 956, 024
Institutions other than health-related schools [2]	81, 653, 633
Total	395, 987, 714

[1] Includes schools of veterinary medicine, pharmacy, nursing, chemistry, and biological sciences.

[2] State, County, and Municipal Health Agencies as well as hospitals and independent research institutions.

Although grants made under this program have ranged from the construction of relatively small additions to existing facilities to the support of all necessary research areas in large medical centers, the trend in recent years has been in the direction of providing large, multipurpose facilities. Specific examples of projects completed during the past year are the following:

Private nonprofit medical schools:	
Stanford University, Palo Alto, Calif.: A 3-story clinical sciences research building	$2, 117, 588
Public medical schools:	
State University of New York (Downstate Medical Center), Brooklyn, N.Y.: Construction of a building for clinical research laboratories	2, 520, 000
University of Texas, Dallas, Tex.: Construction of a new research laboratory building	1, 186, 069
Medical College of Virginia, Richmond, Va.: Construction of research space in a new education building	1, 766, 893
Private nonprofit:	
Salk Institute for Biological Studies, La Jolla, Calif.: Installation of fixed equipment and the necessary utilities in the north wing of the institute laboratory	1, 010, 400
University of Southern California, Los Angeles, Calif.: A complex of four biosciences research buildings	1, 060, 650

The $35,000,000 requested for 1968 would be used to help meet some of the following estimated requirements:

Balance of recommended grants as of June 30, 1967	$85, 700, 000
Applications for fiscal year 1968 councils	65, 000, 000
Total estimated requirements	150, 700, 000

There are no funds requested for construction of centers for research on mental retardation since the authority for this program expires June 30, 1967.

General Research Support Grants

Amounts available for obligation

Appropriation:	Amount
1967	$51,700,000
1968	61,700,000

Obligations by activity

General research support grants:	Amount
1967 estimate	$51,700,000
1968 estimate	61,700,000
Increase or decrease	+10,000,000

Obligations by object

41 Grants, subsidies, and contributions (total obligations):	Amount
1967 estimate	$51,700,000
1968 estimate	61,700,000
Increase or decrease	+10,000,000

Summary of changes

	Amount
1967 enacted appropriation	$51,700,000
1968 estimated obligations	61,700,000
Total change	+10,000,000

	Increase
Program: General research support grants	$10,000,000

EXPLANATION OF CHANGE

The program increase of $10,000,000 will be distributed as follows: $1,500,000 for general research support to the originally supported schools and institutions; $1,500,000 for biomedical sciences support grants and $7,000,000 for health sciences advancement awards.

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".

The Public Health Service Act, Title III, General Powers and Duties of Public Health Service, Part A, Research and Investigation.—

"Sec. 301. (d) Make grants-in-aid. . . . to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their 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 and 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;"

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

ITEM	ACTION TAKEN OR TO BE TAKEN
1967 Senate Report	
(1) The committee directs that the demonstration and service components of the NIMH grant programs be excluded in computing the Institute's contribution to the program for fiscal year 1968 and in determining the grantee institutions' entitlement to general research support grants. The committee also points out that neither the planning nor the operational grants made by the Division of Regional Medical Programs—which is primarily service- rather than research-oriented—should be included in the general reesarch support program calculations.	(1) The demonstration and service components of the NIMH grant programs, and the planning and operational grants made by the Division of Regional Medical Programs will be excluded in computing the contributions to the program for fiscal year 1968 and in determining the grantee institutions' entitlement to general research support grants.

INTRODUCTION

The General Research Support grants program contributes to the development of research capabilities of institutions so that they may become effective partners with the Federal Government in the pursuit of biomedical research objectivies of national importance. This is accomplished by: (1) providing flexible general support to both health professions schools and other university graduate schools and components so as to enhance the effectiveness of the research projects underway at the institution, to redress imbalances in institutional research activities, and at the same time permit the development of institutional objectivies along self-articulated lines; and (2) 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 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 institutional development for the improvement of health research and of the research environment rather than depend on the specifics set out by research grants projects. 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 support of travel of scientists to professional meetings, 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 296 separate awards are now made to schools of dentistry, medicine, osteopathy, pharmacy, public health and veterinary medicine, and to hospitals, research institutes, research fundations, and State and municipal health departments.

Biomedical Sciences Support Grant Program.—This program extends general research support to non-health professions schools. The NIH 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 General Research Support program, as demonstrated by the fact that a significant proportion of NIH 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 components, and that they may have the

same benefits that now accrue to the health professions schools. Approximately 100 institutions are funded under this program in 1967.

Health Sciences Advancement Award Program.—Funds were provided in 1966 to establish a program of grants for health sciences advancement purposes to institutions primarily graduate academic institutions. Unlike the General Research Support program which rewards attained excellence, this new program emphasizes promise and opportunity and is conceived to be a means for providing time-limited support for a well defined effort by the institutions to advance to a new level of achievement in research and research training in the health sciences. Approximately eight health sciences advancement awards will be made in 1967.

DISTRIBUTION OF FUNDS BY PROGRAM AREA, IN 1968

The requested amount of $61.7 million, an increase of $10.0 million, would be distributed as follows: $43.2 million for General Research Support to approximately 310 institutions; $7.5 million for Biomedical Sciences Support Grants to approximately 115 institutions, and $11.0 million for health Sciences Advancement Awards to approximately 22 institutions.

The following table illustrates the 1967–68 distribution of general research support grants as proposed in this estimate:

General research support

	1967 estimate		1968 estimate	
	Number	Amount	Number	Amount
Educational institutions:				
Dentistry	49	$2,468,000	49	$2,550,000
Medical	90	23,719,000	93	24,340,000
Osteopathy	5	171,000	5	179,000
Public health	12	1,797,000	12	1,797,000
Pharmacy	9	475,000	10	490,000
Veterinary medicine	11	1,248,000	12	1,327,000
Noneducational institutions:				
Hospitals	63	6,303,000	66	6,344,000
Research foundations, institutes, and others	55	5,193,000	61	5,839,000
Health departments	2	326,000	2	334,000
Subtotal	296	41,700,000	310	43,200,000
Biomedical sciences support grants	100	6,000,000	115	7,500,000
Health sciences advancement awards	8	4,000,000	22	11,000,000
Total	404	51,700,000	447	61,700,000

REGIONAL MEDICAL PROGRAMS

WITNESSES

DR. ROBERT Q. MARSTON, DIRECTOR, REGIONAL MEDICAL PROGRAMS

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

KARL D. YORDY, ASSISTANT DIRECTOR, DIVISION OF REGIONAL MEDICAL PROGRAMS

JAMES LAWRENCE, FINANCIAL MANAGEMENT OFFICER, DIVISION OF REGIONAL MEDICAL PROGRAMS

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. WILLIAM H. STEWART, SURGEON GENERAL

G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER

JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Personnel compensation:			
11.1	Permanent positions	86	1,186	1,327
11.3	Positions other than permanent	13	40	50
11.5	Other personnel compensation	1	12	23
	Total personnel compensation	100	1,238	1,400
12.0	Personnel benefits	7	103	115
21.0	Travel and transportation of persons	22	90	120
22.0	Transportation of things	4	2	2
23.0	Rent, communications, and utilities	18	30	40
24.0	Printing and reproduction	2	19	34
24.1	Other services	209	371	396
	Project contracts			2,225
25.3	Payment to "National Institutes of Health management fund"	154	431	490
26.0	Supplies and materials	5	14	23
31.0	Equipment	70	50	69
41.0	Grants, subsidies, and contributions	2,066	31,952	80,400
99.0	Total obligations	2,657	34,300	85,314

Personnel summary

	1966 actual	1967 estimate	1968 estimate
Total number of permanent positions	50	135	149
Full-time equivalent of other positions	1	2	4
Average number of all employees	13	128	142
Average GS grade	7.4	7.6	7.7
Average GS salary	$7,915	$8,394	$8,466

Program and financing

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	Program by activities:			
	1. Grants for regional medical programs	2,066	31,952	80,400
	2. Direct operations:			
	(a) Professional and technical assistance	142	613	2,968
	(b) Review and approval of grants	131	723	816
	(c) Program direction	294	1,012	1,130
	Total, direct operations	567	2,348	4,914
	Total program costs, funded [1]	2,633	34,300	85,314
	Change in selected resources [2]	24		
10	Total obligations	2,657	34,300	85,314
	Financing:			
16	Comparative transfer from other accounts	−104	−356	
21	Unobligated balance available, start of year		−21,934	−21,000
24	Unobligated balance available, end of year	21,934	21,000	
25	Unobligated balance lapsing	513	11,994	
40	New obligational authority (appropriation)	25,000	45,004	64,314
	Relation of obligations to expenditures:			
10	Total obligations	2,657	34,300	85,314
70	Receipts and other offsets (items 11-17)	−104	−356	
71	Obligations affecting expenditures	2,553	33,944	85,314
72	Obligated balance, start of year		2,248	28,654
74	Obligated balance, end of year	−2,248	−28,654	−76,157
90	Expenditures	305	7,538	36,811

[1] Includes capital outlay as follows: 1966, $47,000; 1967, $50,000; 1968, $69,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1966, $24,000; 1967, $24,000; 1968, $24,000.

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. FLOOD. We now have the regional medical programs about which we have heard a great deal down through the months. We have Dr. Robert Q. Marston, Director, regional medical programs.

We have a biographical sketch of Dr. Marston which we shall insert in the record at this point.

(The biographical sketch follows:)

Name: Robert Q. Marston.
Position: Associate Director, National Institutes of Health, and Director, Division of Regional Medical Programs.
Birthplace and date: Toana, Virginia, February 12, 1923.
Education: B.S., Virginia Military Institute, 1943; M.D., Medical College of Virginia, 1947; B.Sch. Oxon.), Oxford University, 1949; Intern, Johns Hopkins University, 1949–50; Assistant Resident, Vanderbilt University, 1950–51; Assistant Resident, Medical Colege of Virginia, 1953–54.
Experience: Associate Director, National Institutes of Health, and Director, Division of Regional Medical Programs, 1966–Present; Vice Chancellor, University of Mississippi, and Dean, School of Medicine, 1965–66; Director, University of Mississippi Medical Center, and Dean, School of Medicine, 1961–65; Associate Professor of Medicine and Assistant Dean in Charge of Student Affairs, Medical College of Virginia, 1959–61; Assistant Professor of Bacteriology and Immunology, University of Minnesota, 1958–59; Assistant Professor of Medicine, Medical College of Virginia, 1954–57.
Association memberships: American Medical Association, Association of American Medical Colleges, American Association for the Advancement of Science, American Federation for Clinical Research.
Special honors: Rhodes Scholar, 1947–49; Markle Fellow, 1954–59.

Mr. FLOOD. I see you have a statement, Dr. Marston. Do you have any backup people you want to introduce?

Dr. MARSTON. Mr. Yordy, the Assistant Director of the Division of Regional Medical Programs is on my left, and Mr. Lawrence, behind me, is the budget officer for the Division.

Mr. FLOOD. And over to the far left you have?

Dr. MARSTON. Dr. Shannon.

Mr. FLOOD. All right. Go ahead.

GENERAL STATEMENT

Dr. MARSTON. Mr. Chairman and members of the committee, a year ago I appeared before you on behalf of the regional medical programs for heart disease, cancer, stroke, and related diseases which were authorized by Public Law 89–239 only a few months previously in the fall of 1965. Now, 1 year later, you will be pleased to know that planning grants involving more than 80 percent of the population have been approved by the National Advisory Council. We are currently reviewing applications which will move this figure to over 98 percent of the population of the country. Four grants for initial operational activities have been awarded. Deeply involved in these activities are individuals representing the health professions, institutions, and organizations in these regions.

I would like to call your attention to some of the objectives and plans outlined a year ago as a background against which to discuss the progress made during the last year and the plans for future action as the Nation moves into an even more vigorous phase in the implementation of this program.

REGIONAL COOPERATIVE ARRANGEMENTS

The principal purpose of this important new program is to provide the medical profession and the medical institutions of the Nation greater opportunity to make available to their patients the latest advances in the diagnosis and treatment of heart disease, cancer, stroke, and related diseases. This overall objective is to be accomplished through the planning and establishment of regional cooperative arrangements among medical institutions which can serve as the framework for linking programs of research, training, continuing education, and demonstration activities in patient care conducted by medical schools, medical organizations, research institutions, and hospitals. The regional cooperative arrangements are intended to assure close contact between the development of new medical knowledge and techniques in the environment of research and teaching and the delivery of high quality patient care in the hospital environment.

There are a number of long-range factors and trends which led Congress to authorize this program. The most important of these factors is the impact of science on the nature of medicine and medical practice. The dynamic growth of medical research in this country during the past 20 years and the resulting advances in knowledge form a scientific base which is the beginning point for regional medical programs. Some of the other factors include the 40-year discussions on regionalization of medical services, the evolution of the medical schools with the accompanying development of great medical centers, the increase and upgrading of hospitals and health facilities with assistance from the Hill-Burton program, and the underlying social factors relevant to health concerns, including the rising expectations of the consumer of health services who increasingly is coming to expect modern medical science to have the solutions to his health problems.

REPORT ON HEART DISEASE, CANCER, AND STROKE

Over the years many public and private studies have been concerned with the problems this program seeks to solve. However, the immediate impetus for the introduction of legislation was the publication of the report of the President's Commission on Heart Disease, Cancer, and Stroke which focused on the relationship between science and service in medicine. The needs which were stressed by the President's Commission are in fact a statement of the great opportunities that exist for the improvement of the health of the American people.

This committee, Mr. Chairman, deserves a full measure of the credit for the development of these opportunities. It is because we've seen the development of a great biomedical research effort, including the provision of modern medical facilities and the development of increased training opportunities for medical personnel, that we can seek to make more widely and promptly available the results of progress.

The goals and purposes of regional medical programs represent unquestioned basic human needs. More than any other program I know, the primary question is not whether it would be good to have such programs but rather how well can they work. A detailed special progress report has already been submitted to the committee. It

reviews the basic nature of the regional medical programs and their progress during the past year, and it summarizes the issues which will be dealt with in greater detail in the Surgeon General's report to the President and Congress required by law to be submitted by June 1967.

IMPLEMENTING THE PROGRAM

Public Law 89–239 was enacted and signed by the President in October 1965. The Division of Regional Medical Programs was authorized in December 1965 and the first meeting of the National Advisory Council was held the same month. The Division was established and the first staff arrived February 1, 1966. The National Advisory Council met approximately every 2 months; that is, twice the normal number of meetings for councils in order to supply the advice needed. In January 1967 we held a meeting of some 650 of the most important people from all areas of the health fields, from all parts of this country to give us the necessary grassroots information for the report which the Surgeon General must make this summer.

Even before the law was passed, many groups in the country had started the preplanning necessary to submit an application for a planning grant. By January 1, 1967, 48 planning grant applications requesting more than $30 million had been received. In addition, applications from four regional medical programs for operational pilot projects were also received requesting almost $12 million.

Mr. FLOOD. For what?

Dr. MARSTON. Operational pilot projects. This is a term from the law. The operational grants are defined in the law as pilot projects.

Forty-four planning grants have already been approved by the National Advisory Council, representing an investment of almost $20 million in Federal grant funds for the first year of planning activities.

The 44 planning grant applications encompass more than 80 percent of the population and, as I stated earlier, we have under review applications raising this percentage above the 98-percent figure. It is fair to say at this time that this Nation has started a new health program.

Applications have received intensive review by experts in health, education, and community affairs from all sections of the country and finally by the National Advisory Council as required by law. Although intensive review has resulted in less rapid expenditure of funds, it has assured a clearer definition of objectives and mechanisms and it has created confidence in the regional medical programs.

I would not like to give you the idea that all of this has been accomplished without having serious questions raised during the past year. The legislation which created regional medical programs is being implemented during a period of uncertainty in the health field. There are problems of limited health manpower to meet the increasing needs and demands for health services. Indeed, one of the main objectives of this program is to achieve better utilization of all health resources, particularly manpower. There are problems of adaptation to changes which are outgrowths of both the needs leading to the establishment of regional medical programs and the current enactment of other broad legislation in the health field such as medicare. There is at the same time the increasing need to relate national objectives more closely to the specific problems of local areas and regions. It is against this

background plus the very magnitude of the aspirations of this program that this progress should be viewed.

REGIONAL ADVISORY GROUPS

A year ago there was suspicion that some national master plan was about to be imposed upon the Nation. Groups that were not accustomed to working closely together were concerned with the prospect of such new relations. However, the type of cooperative arrangements which are being developed to link science and service are evoking an unexpected and unprecedented degree of enthusiasm, excitement, and action. We hear evidence of this in what people are telling us, we see it in the commitments being made by individuals, organizations, and institutions, and we recognize it in the development of new groups with potentially great influence for good, the regional advisory groups which are broadly representative of the health, medical, and civic organizations of the regions. A typical regional advisory group has the follownng composition: 21 percent are practicing physicians; 18 percent are associated with medical schools and affiliated hospitals; 13 percent are from cancer societies, heart associations, and other voluntary health agencies; 12 percent are administrators of hospitals; 8 percent are nurses and other health workers; 8 percent are from public health departments; and 14 percent represent the public at large.

Mr. FLOOD. Are you talking about heart, cancer, and stroke only?

Dr. MARSTON. The regional medical programs for heart, cancer, and stroke.

Mr. FLOOD. That is all you are talking about?

Dr. MARSTON. And related diseases.

Mr. FLOOD. What does that mean?

Dr. MARSTON. The legislative history identified two related diseases. One was diabetes and the other was kidney disease, and the point was made in order to work effectively against heart, cancer, and stroke one cannot exclude closely related diseases such as diabetes, which is related to the arteries, and kidney disease, which is related to the cardiovascular system.

These groups I have just enumerated vary in size but of the applications we have received to date, which essentially cover the country, as I have said, these represent some 1,500 individuals who are serving on regional advisory groups or an average of about 30 per region.

Mr. FLOOD. Do you have any of the antipoverty people on these committees?

Dr. MARSTON. There have been representatives from groups who are interested in the program.

Mr. FLOOD. There could be?

Dr. MARSTON. Yes, sir.

The State health officer of a Western State said recently that for the first time in his 26-year career he saw the representatives of all of the major health resources in his area sit down to discuss problems they had in common. The president of a State medical society in the Midwest told me that for the first time in his experience, his colleagues had been stimulated and encouraged to think seriously as a group about how the services to all patients—not only their own individual patients but all patients in the area—could be improved. A practicing physician in one of the Rocky Mountain States told me he viewed this

program as the most important and exciting development in the health field in his time. Important institutions, influential organizations, and professional and civic leaders are making serious commitments to the program.

Mr. FLOOD. What do you mean by "serious commitments"?

Dr. MARSTON. Well, they have accepted and have made commitments in terms of time——

Mr. FLOOD. Who have?

Dr. MARSTON. The hospital associations——

Mr. FLOOD. I know that but who are the other people?

Dr. MARSTON. The medical schools in the area and the practicing physicians. Community organizations have been interested.

Mr. FLOOD. What do you mean by that?

Dr. MARSTON. Two of the voluntary health associations, the American Heart Association and the American Cancer Society, are seeking ways in which those organizations can work on the community level more closely. There have been representatives from labor groups in some areas that have accepted positions on the advisory groups and have worked with the committees on the development of programs. There have been representatives, of course, from the State health officers' associations.

Mr. FLOOD. Is this a merely nominal committee which meets in some big city with a great medical complex of six hospitals and nine clinics and whatnot?

CONSULTATION WITH GROUPS IN THE REGION

Mr. LAIRD. They have an all-day meeting. They throw a lot of stuff at them in a short time and at 4 o'clock they ask if there are any questions. This has happened in State after State.

Mr. FLOOD. That is the old army game. Any questions? Bang.

Mr. LAIRD. The whole group meets four to eight times but they have the program so well planned that there is not much of a chance for questions.

Mr. FLOOD. I am glad you are worried. This is what worries me, Doctor. There is this tremendous medical complex in Philadelphia which is one of the greatest in the world—hospitals, clinics, and whatnot—and this is exhibit A. They received a grant of $1.5 million to do something. But the thing that concerns me, Doctor, and Mr. Laird is suggesting the same thing—are the provinces represented or are you giving the peasants a fait accompli? Do you have meetings of very important people at these great centers and then do you go out to what I call a subregion—you didn't, I did—and do you talk to the heads of the medical societies in my subregion? Do you talk to the hospital administrators? Do you talk to the nurses? Do you talk to all of these people who should be on your committee and who are not? The thing that worries me—and I am sure Mr. Laird is suggesting the same thing although I do not speak for him—is that you have gone ahead and set up these regions without consulting anybody outside of this great center. Then you notify the rest of the people that the region has been set up, without consultation. Nobody has talked to them or seen them but they pick up a paper one day and see you have created a region and they are in it. What about that, Doctor?

Dr. MARSTON. I think there are two things. One of the purposes of the planning grant is to define more clearly and accurately what the region should be.

Mr. FLOOD. If you do not it will die aborning.

Dr. MARSTON. Yes, sir. We have asked repeatedly and have returned applications for evidence of broader representation geographically and among groups in the region.

Mr. FLOOD. Am I saying about what you had in mind, Mr. Laird?

Mr. LAIRD. Just about. I know of several of the groups which had meetings and they all follow the same pattern. They bring in this massive group representing physicians, hospitals, various citizens' health groups, and nurses, and set up a broad program for them.

Mr. FLOOD. Do you mean in the big center itself?

Mr. LAIRD. In the region. Then these people start filing applications for Federal money, rather than doing any real planning. It looks to me that many of the applications will be for the same thing we have been funding or should be funding through regular NIH categorical institutes.

Dr. SHANNON. If I may comment, I see it in a somewhat different way than Dr. Marston has seen it. There are two purposes served by these meetings and one purpose that is not served. I would like to emphasize the purpose that is not served. The purpose of these meetings is not to go to the region and attempt to resolve all the conflicts that may exist between different professional groups. The purpose is to explain the order of magnitude of funds available under the legislation, the functions that can be supported, and to indicate the character of the representative body that is necessary for the program to interact among the different groups. As I have observed the operations of Dr. Marston's Division, repeatedly the applications that have come in have shown a lack of broad group representation or they have shown a lack of geographic representation. In either of these cases, the applications have been returned to the region with the comment that they do not truly represent the region. When an application is accepted, it is hoped and believed that the planning group given the responsibility to plan will be a well-informed, small group of knowledgeable people who can turn to the different elements in their region and resolve some of the problems. This is the primary channel of information to the local people. There are 50-State and I do not know how many county medical associations and hospitals; if one attempted to make contact with each of the elements of this complex society one could not do the job.

Mr. LAIRD. It would be impossible.

Mr. FLOOD. What about the rule of reason?

Dr. SHANNON. The rule of reason is that you have to have a local group well-constituted and well-informed which will serve as an agent, if you will, to discuss and evolve a program that will meet the needs of that region—and they are peculiar wherever one goes.

PROLIFERATION OF GRANT REQUESTS

Mr. LAIRD. Mr. Chairman, I think he misses the point of my criticism, if you want to call it criticism. What bothers me is to have 150 or 200 requests directed to this regional group from people all over the State. If you start doing work in this way not only does it put this

subcommittee in a bad position because you will not be able to fund these 250 requests that come in, but it is impossible to have a good coordinated program this way.

Dr. SHANNON. I asked Dr. Marston to find out specifically how this thing got off the track in Wisconsin. I do not know the answer to this because I have not had a chance to talk to him about it. It is not the purpose of this program to establish some petty bureaucrats within each region who will then disburse Federal funds to satisfy the individual needs, as they are viewed by the individual practitioner, but rather to evolve a comprehensive system of services that will lessen the disparity between the excellence of university complexes and the local hospitals. This requires a great deal of planning by and assistance from all medical elements in the region. In the final analysis, we will have to work with some responsible group that represents the region and I am sure that as they programs evolve, one of Dr. Marston's problems will be to resolve complaints that come from subareas.

Mr. FLOOD. By the way, if you will yield, we are talking about the same thing only I am going a bit further than Mr. Laird. My insistence is that this mother hen, the region, does not do a thing until she has talked with all her chicks. If you do that you will not get this proliferation of grant requests, because they have been told in advance this is not Santa Claus, this is no handout, and don't come in with all these applications. If you do that you will not have a problem.

Dr. SHANNON. Mr. Laird may not, but we will. What we want to do is to minimize these problems.

Mr. FLOOD. There is only one way to do it. Go out in the provinces and talk to them and tell them and they will work with you. If you do that Mr. Laird will not have a problem.

Dr. SHANNON. Mr. Chairman, I could not agree more but the first step is to have a well-organized central group that represents the major elements in the region and who can accept executive responsibility for program development. This group should be developed with full appreciation of all the elements in that region. Then, having applied for planning funds, they must immediately find out the potentials, and capabilities, the desires and the willingness of all the elements.

Mr. FLOOD. I agree with that.

Dr. SHANNON. But Dr. Marston had a difficult time in summarizing how these programs have operated to date. The first planning grant, as I recall, was made in January?

Dr. MARSTON. July for planning grants.

OPERATIONAL GRANTS

Dr. SHANNON. When was the first operational grant made?

Dr. MARSTON. The first operational grant was made last week.

Dr. SHANNON. These first operational grants should not be viewed as full-blown regional operational grants.

Mr. LAIRD. How much was the first grant for?

Dr. MARSTEN. Approximately $900,000.

Mr. LAIRD. Where did it go?

Dr. MARSTON. The Albany region for $900,000; one to Missouri for approximately $2.5 million; one to Kansas for approximately $1 million; one to the intermountain region, Utah and surrounding States, for approximately $945,000. There is a second phase of that which has required additional study.

I think the evaluation of these operational grants in one sense answers your questions, Mr. Laird, because the first thing said is that a series of projects does not constitute an operational grant; there must be evidence of an overall strategy, evidence of the type of leadership that is on board and can carry forth the proposals in the operational grant.

Mr. LAIRD. You are talking along my line.

Dr. MARSTON. This is one reason we have been on these operational grants for 6 months.

Mr. FLOOD. He is talking along my line.

Dr. MARSTON. The first consensus before we look at a project is whether they have the organization, the structure, the commitments from the institutions, and not just the big ones, and a broad strategic approach.

Mr. FLOOD. That is a good term. It sounds like McNamara.

Dr. MARSTON. This is by the law, too.

Mr. FLOOD. Mr. Laird and I have worked on defense the last 10 or 15 years. We are not amateurs in this business.

Dr. MARSTON. I know, sir.

Mr. FLOOD. Well, here is the problem, Doctor. Are you a fisherman?

Dr. MARSTON. Yes, sir.

Mr. FLOOD. Well, so am I. And if you ever saw a trout go for a fly I went for this program a year or two ago when I heard the President make a speech one night to a joint session. Then I came back down here to the hearings a couple weeks later and discovered it was not the same program at all.

Dr. SHANNON. May I comment on your fisherman's experience?

Mr. FLOOD. I took that hook, line, and sinker and I was wrong.

Dr. SHANNON. You are interested in fishing and we are interested in catching fish. By that I mean that we will use worms, we will not limit ourselves to flies.

What I really mean to say is that we are interested in what the catch is and that we will use any device within the law and propriety to achieve that end.

Mr. FLOOD. Doctor, I walked out of that joint session at 10 o'clock that night anticipating that we would have centers in our hometowns that would take care of heart, cancer, and stroke patients. I was completely wrong, and I think the President was perhaps mislead a little. I think he and I thought the same thing.

Mr. LAIRD. That costs money, though.

Mr. FLOOD. That was not it. I came here 2 weeks later and found it was a different thing altogether. Do you see the shock?

Dr. SHANNON. Yes, I do. I would point out that if we bulled through this thing without solving some of the problems you and Mr. Laird have alluded to, we would tear the fabric of the local base of medical services without being able to substitute an effective alternative for it. Our purpose is to provide a mechanism that accepts the present system of services but permits the achievement of a higher degree of excellence. This will not move as rapidly as we would like it to move.

Mr. FLOOD. I have no quarrel with that. I accept that as absolutely right except I want to be sure you go out and talk to the people where I live before you decide anything. I know these prima donnas in the great hospitals. I know the beaux gestes in these great complexes. They look down their noses at their brothers 50 miles away.

PREVIOUS POSITIONS OF OFFICIALS IN THE REGIONAL MEDICAL PROGRAM

Dr. SHANNON. It might be helpful if Dr. Marston could introduce in the record the commitments people have made to these programs, the program directors who have moved out of the conventional framework of their professions into total involvement in this program. It might be worthwhile if he indicated what the men were doing before, because these are individuals with great dedication who moved out to be of broader service.

(The information follows:)

Previous positions of officials now providing full-time leadership of regional medical programs

Region	Title	Name	Previous position
California	Program coordinator.	Ward, Paul D.	Administrator, State health and welfare agency, California.
Central New York	do	Lyons, Richard H., M.D.	Professor and chairman, department of medicine, Upstate Medical Center, Syracuse.
Colorado-Wyoming	do	Hildebrand, Paul R., M.D.	Private parctice of medicine; former president, Colorado Medical Society.
Connecticut	do	Clark, Henry T., Jr., M.D.	Vice president for health and medical affairs, University of North Carolina.
Hawaii	Deputy director.	Graham, William D., M.D.	Director of Hospital Research, Veterans' Administration, Washington, D.C.; major general (U.S. Army, retired).
Intermountain	Program coordinator.	Castle, C. Hilmon, M.D.	Associate dean, University of Utah Medical School.
Kansas	do	Lewis, Charles E., M.D.	Associate dean, University of Kansas Medical Center.
Louisiana	do	Sabatier, Joseph A., M.D.	Private practice of medicine; president, State medical society.
Maryland	do	Turner, Thomas B., M.D.	Dean, School of Medicine, Johns Hopkins University.
Memphis, Tenn.	do	Culbertson, James, M.D.	Professor of medicine, University of Tennessee College of Medicine.
Metropolitan Washington (District of Columbia).	do	Mattingly, Thomas W., M.D.	Private practice of medicine; chairman, department of medicine, Washington Hospital Center.
Missouri	Program director.	Wakerlin, George E., M.D.	Medical director, American Heart Association.
Mountain States	Director	Popma, Alfred M., M.D.	Chief of radiology, St. Luke Hospital, Boise, Idaho.
Nebraska-South Dakota.	Program coordinator.	Morgan, Harold S., M.D.	Private practice of medicine.
North Carolina	do	Musser, Marc J., M.D.	Deputy Medical Director, Veterans' Administration, Washington, D.C.
Ohio Valley	do	McBeath, William H., M.D.	Director of medical care, Kentucky Health Department.
Rochester, N.Y.	do	Parker, Ralph C., Jr., M.D.	Clinical associate professor of medicine, University of Rochester School of Medicine and Dentistry.
Tennessee mid-South	do	Olson, Stanley W., M.D.	Dean, School of Medicine, Baylor University.
Washington-Alaska	do	Sparkman, Donald R., M.D.	Medical director, division of vocational rehabilitation, State of Washington.
Western New York	Program director.	Ingall, John R. F., M.D.	Associate cancer research surgeon, Roswell Park Memorial Institute, Buffalo.
Wisconsin	Program coordinator.	Hirschboeck, John S., M.D.	Vice president and dean, Marquette University School of Medicine.

EXAMPLES OF REGIONAL MEDICAL PROGRAMS

Mr. FLOOD. May I also suggest this, Doctor. Suppose you take two of your prize programs and describe them for the record.

Dr. MARSTON. In the record?

Mr. FLOOD. Yes, not now but at your convenience.

Dr. MARSTON. I will appreciate this opportunity.

(The information follows:)

Summary of Activities in Two Regional Medical Programs

MISSOURI REGIONAL MEDICAL PROGRAM

Following the first phase of planning activities under a grant from the Division of Regional Medical Programs effective July 1, 1966, the Missouri Region utilized the results of its own planning undertaken prior to the planning grant and submitted its proposal for an operational grant. The operational grant was awarded on April 17, 1967, in the amount of $2,493,841 for the first year of activity. This Program involves to an extraordinary degree all organized medicine and osteopathy, hospitals, official state health agencies, 19 voluntary health agencies, and the University of Missouri where 25 representatives of the School of Medicine, the College of Engineering, the Department of Economics, the Department of Sociology, the School of Education, the School of Journalism, and the extension service are actively involved in the Program. Headquartered as it is at the University of Missouri in Columbia, the Program is expected to benefit as a result of the working relationships this land grant college has with all areas of the state through its extension programs which provide effective outlets for all of its activities, and these can now include certain aspects of the Regional Medical Programs.

The leadership of the Missouri Regional Medical Program is being provided by Dr. Vernon Wilson, Dean of the School of Medicine, who is devoting part of his time to being overall program coordinator, and Dr. George Wakerlin, who is the full-time program director. Dr. Wakerlin came to the Missouri Regional Medical Program from his former position as Medical Director of the American Heart Association. The development of this Program has also benefited from the active involvement of a regional advisory group, representative of the major health interests in the Missouri Region as well as members of the public. The regional advisory group carried out the statutory requirement of approving the operational grant application only after extensive discussion of the application. The advisory group has met eight times in the first year of the Program's activity and was also involved in the negotiations leading up to the operational grant award. The site visit by members of the national review groups and staff of the Division of Regional Medical Programs during the review of the operational grant application specifically explored the role of the regional advisory group including discussion with members of the advisory group. This discussion provided convincing evidence of effective involvement of the regional advisory group.

During the implementation of operational programs, the planning activities will proceed with the development of proposals for extending the program to other areas in the Missouri Region and the exploration of new program activities that can be included in subsequent applications.

The Missouri Program is characterized as having a general objective of the early detection and competent treatment of heart disease, cancer, stroke and related diseases. "All endeavors," according to the application, "will be oriented toward maximizing the amount of diagnosis and care which can be delivered in the patient's home and community by the physician and the local medical resources while maintaining and improving the quality of medical effort and a reasonable balance between medical cost and economic gain to the individual and his home community."

To achieve these objectives, more than 20 interrelated projects will be conducted under operational program.

PROPOSED ACTIVITIES

The Smithville community

The anticipated collective impact of the operational projects on the town of Smithville, a small western Missouri community of 3,500 with both rural and suburban influences, is an example of how coordination of the necessary professions, agencies, and facilities can provide the high quality of health services needed in such places.

Approaches which are planned to provide a health care system that will also insure that a maximum number of the local patients can be cared for in the Smithville community include some 8 areas of activity—

Automated clinical laboratory testing for multiphasic testing.

Automated patient history system for physicians to obtain complete medical history before seeing the patients.

Simulation (computer modeling) systems for early detection of heart disease, cancer, and stroke.

Computer fact bank which can display the results of multiphasic laboratory screening of the physician's patients on an audio-visual machine.

Studies to identify how people are using health services.

Studies to determine the degree to which health problems of selected groups of people apply to the general population.

Exploration of the possibility of automated electrocardiography service in Smithville Hospital connected with University of Missouri Medical Center for rapid, accurate transmitting, receiving and interpreting of electrocardiograms.

Uilization of methods to educate and encourage physicians and paramedical personnel in the use of multiphasic screening studies, population surveys, automated information and retrieval systems, advanced computer simulation models and automated data retrieval systems.

In addition, several other types of major projects will be undertaken—

A communications research project will be undertaken to make participation by the general public more effective in the regional medical programs by identifying attitudes, opinions, beliefs and misconceptions about heart disease, cancer, and stroke. It will also identify the courses of action most acceptable and production will be conducted.

A bioengineering project as a clinical device will provide technical assistance in the evaluation and development of sensor-transducers for early detection of heart disease, cancer, and stroke; as a research device, it will generate basic information which will measure physiological parameters which may help to establish a system by which the early detection of heart disease, cancer and stroke can be achieved.

Other projects are—

Mass X-ray screening for these diseases.

Design for operational research system to attempt to identify information on diagnosis and treatment.

Automation of hospital records.

Expansion of comprehensive cardiac care unit in Southwest Missouri to serve as a model for the development of such capabilities in areas remote from large medical centers.

Development of listing of all health services.

Study of health among selected population groups.

Evaluation center.

Central administration.

KANSAS REGIONAL MEDICAL PROGRAM

The Kansas Regional Medical Program also received a planning grant effective July 1, 1966. This Regional Program has gone through an initial planning phase and completed and submitted its operational application. The operational grant was awarded on April 12, 1967, in the amount of $1,076,600 for the first year of activity. The Kansas Region also utilized planning that had preceded the award of the planning grant. This application includes three representative characteristics of the first Regional Medical Programs.

First, it capitalizes on the strengths of the existing programs of education and training that are already in operation within the Kansas Region. The primary emphasis of the proposal is the expansion and upgrading of skills of health personnel by an extension of these programs. It is also intended that these resources will be shared with the adjacent Missouri Region, and later with other regions.

Secondly, it proposes the development of an affiliated medical center in a remote community to implement such programs, and a study of this approach to evaluate its effectiveness as a prototype.

Thirdly, activities in the region's one major metropolitan area are proposed to serve as the source of developing new programs in heart disease, cancer, stroke and related diseases that can be translated into educational and training activities and, when ready, be added to the existing activities in the outlying areas and at the affiliated medical center.

Both the Kansas and Missouri applications were also developed with particular attention to interregional cooperation along their borders and particularly in the Kansas City area.

The Kansas Regional Medical Program will be directed on a full-time basis by Dr. Charles Lewis who has been Professor and Chairman of the Department of Preventive Medicine and Community Health at the Kansas University Medical Center. The regional advisory group played an active role in the development of the program. It met five times, carefully considered the operational grant proposal, and approved the grant application. The role of the regional advisory group again was specifically discussed during the review of the application by the National Advisory Council and was explored during the site visit.

During the initial operational activities the planning activity will continue to develop the basis for the extension of the program to other areas within the Kansas region and to develop new operational activities.

PROPOSED ACTIVITIES

Affiliated education center—Great Bend, Kansas

In order to teach the latest advances to physicians, nurses, technicians and other health personnel who work at considerable distances away from the University Medical Center, an affiliated medical center will be established in a new 230-bed hospital in Great Bend, a community of 20,000 people, 250 miles west of Kansas City. Not only will this keep them as close to their home communities as possible during the instructional period, but teaching programs can be developed to meet their individual needs.

Activities that will take place at this center to upgrade levels of professional competence—

Clincial traineeships for physicians and other health personnel.

Teaching laboratory for training medical technologists.

An audio-visual training center where other self-learning devices are also available.

A close relationship with the Health Science and Information Center at the University Medical Center where teaching materials and studies will be developed.

Two-way radio, television, xerography, and computer communication with the University Medical Center and other medical centers in the region.

Many projects to be expanded and undertaken in the metropolitan areas are—

Studies of types of physicians and patients who have used the cancer detection clinic; the effectiveness of follow-up of pre-malignant and malignant conditions; and reasons why patients and physicians use or do not continue to use the clinic.

Intensive community-wide efforts to determine working capacity of cardiac patients to encourage more useful living and working programs for them consistent with new medical knowledge of cardiac potentials. This will also include approaches to physicians, union and industrial leaders to determine the most efficient methods to achieve this goal.

Interregional cooperation will include—

Kansas Region will field test and evaluate Missouri Region techniques for early detection of disease.

Missouri will depend upon Kansas experience for programs and facilities to carry out some of its major continuing education efforts, including those of television, radio and production of films.

Initial attempt to develop a regional library resource.

Selection of joint reference panel of national experts in the health care field to assist in integrating the two Programs.

Selection of other consultants to work with both Regions on their joint technical programs.

Joint evaluation and research activities to be planned and carried out by Program evaluation group at Missouri and research and evaluation group at Kansas.

Both medical centers have appointed members to a joint committee to meet regularly for solving problems of mutual concern affecting areas relative to but outside the purview of their Regional Medical Programs.

Investigators and scientists in the cardiovascular-renal field in the metropolitan Kansas City, Missouri and Kansas are involved in discussions of mutual operational research interest.

DISILLUSIONMENT WITH PROGRAM

Mr. FLOOD. This thing got off to a horrible start. It was misunderstood, confused, and did not get off the ground, so we are gun shy.

Mr. LAIRD. There is a lot of disillusionment with it, I think, Mr. Chairman, in that the promise of the program and the promise of the assistance that would be available not only from the Federal Government but from the State governments has not materialized. The program level will be about one-sixth of what was talked about by Dr. Marston and the Surgeon General and the Secretary of HEW and the President of the United States. There has been a lot of misleading information about this program and it comes back to haunt the Congress. The executive branch of the Government put out this kind of misleading information. Our committee was not guilty of that. Certainly a lot of people had their hopes up for this program, and those hopes have been deflated within the past several months. Do you not agree?

Dr. MARSTON. I think the question of the commitment of these people and institutions is related to the dollar figure; yes.

Mr. LAIRD. But I think a lot of people who left the jobs they had to come into this program have been disillusioned. They thought it was of more importance and of greater significance than now appears.

Dr. SHANNON. The real impact of the program is not our determination, Mr. Laird, it is yours.

Mr. LAIRD. I understand that, but we have to have the support of the Secretary of HEW, the President of the United States, and the Surgeon General and you. Many people that went into this program went into it with the understanding that this was probably going to be a program of half a billion dollars. When the President signed the bill at the White House I was there, and every indication was again given to the American public that that was the magnitude of this program. He handed out a lot of pens, it was a wonderful ceremony, but it was almost as misleading as the state of the union message. You can throw the ball back as much as you want, but there were people that were misled as far as this program is concerned.

Mr. KELLY. I would like to comment.

CONGRESSIONAL SUPPORT FOR THE PROGRAM

Mr. FLOOD. Let me comment before you do. That does not mean that this program does not have the support of the Congress and of this committee. There has been a feeling of having been let down for various reasons. However, there is no reason this cannot be done. But the only way it can be done is along the lines Mr. Laird and I happened to suggest. I think you agree there has been an appalling lack of rapport, and we are a year late. But this kind of thing can be done and must be done.

ADMINISTRATION'S POSITION ON THE PROGRAM

Mr. KELLY. Mr. Laird, I do not think the budget that is before you indicates a lack of support on the part of the administration of this program, nor was there an intention to mislead. I think the facts are that the optimism that was generated when the program was launched led people to believe you could move more rapidly in putting a pro-

gram of this magnitude and complexity together than the actual facts have demonstrated. Therefore the program has moved more slowly in order that the basic planning can be more profoundly and thoughtfully done. The program has not been moved to the point of being operational without an adequate basic planning for the program. I think the problem is an element of time for achieving the program and not a lack of support by the administration.

Mr. LAIRD. Mr. Chairman, I must make one comment to our distinguished friend from the Department of Health, Education, and Welfare, Mr. Kelly. That is that the Secretary of HEW does not agree with you. He went to the Bureau of the Budget and asked for $140,600,000 and he supported that request although the NIH came to the Secretary for $202,799,000. The Secretary did go to the Bureau of the Budget and to the President of the United States at a program level much higher than was approved, the $64,314,000. So I say that there were people who were at the operational level of this program who felt the program could move along in 1968. Your statement is a fine statement in support of the Bureau of the Budget position but it is not a good statement so far as supporting the Secretary of HEW or supporting the people working in this program and who have worked in it since its inception.

Mr. FLOOD. That is why we have these hearings. That is why we are saying the things we are saying now so that he who runs may read. As of this minute there can be no doubt any longer this must work.

Mr. KELLY. The Secretary did submit a larger budget in June or July. But by the time it reached the point where we had made decisions on anti-inflationary steps and the 1968 budget, it was clear the kind of budget he was talking about in June was not achievable. The general order of magnitude of this program is such that the progress is necessarily slower than we had anticipated it would be.

Mr. LAIRD. That is why you are down to $64 million?

Mr. KELLY. Yes. As a result, the program will be about $94 million in 1968 because in addition to the $64 million it is anticipated we will carry forward about $30 million in 1967 funds.

Dr. MARSTON. $21 million.

Mr. KELLY. Excuse me, $21 million.

Mr. FLOOD. Dr. Marston, I have the impression you were interrupted.

Dr. MARSTON. I had reached the point of mentioning the institutions, organizations, and professional and civic leaders who are making serious commitments to the program.

Those who have accepted the full-time responsibility for coordinating programs, represent a cross section of "Who's Who in American Medicine." They include persons with experience in high positions of great responsibility such as university vice presidents for health affairs, key administrators of health programs in the Federal Government, chief officers of national voluntary health organizations, elected officials of professional organizations, recognized health planners, and experienced officials in State government. The attraction of this high level of individual capability and institutional and organizational commitment is especially significant since this program involves the basic concept of decentralization by the delegation of an appropriate degree of responsibility for decisionmaking to the regions

themselves. There has been much recent discussion in the Congress and throughout the Nation of the need for some decentralization of responsibility for activities financed with Federal funds. In the case of regional medical programs this decentralization is inspired by neither political nor abstract administrative considerations. Its sole purpose is the achievement of greater effectiveness in carrying out the purposes of the program. Like democracy this approach requires faith in the competence and wisdom of the participants and must allow for occasional achievements that fall short of ideal goals. In the regional medical programs, this faith is justified by the caliber of the institutions, organizations, and individuals who have become involved on the local level. In addition, the effectiveness of the individual programs will be monitored and evaluated systematically at both the regional and national levels to uncover deficiencies.

EARLY OPERATIONAL PROGRAMS

The purpose of plannng is to establish regional medical programs. The National Advisory Council recently recommended the approval of applications for pilot projects in four regions of the Nation, the Albany (N.Y.) regional medical program, the Missouri regional medical program, the Kansas regional medical program, and the Intermountain regional medical program. Grant awards have been made to these regions. It is important to emphasize that the activities and relationships are not limited to State borders.

Our review committees and council worked for more than 6 months in the evaluation of the applications for these pilot projects. While I will be happy to answer questions concerning specific activities proposed, I would like to emphasize that a regional medical program must be more than a collection of projects. The review process has focused on three general characteristics of the proposals. The first focus is on those elements of the proposal which represent the applicant's concept of his regional medical program. In this way, the applicant must indicate that he has a unifying concept for choosing priorities; that there is an effective administrative and coordinating system in which the major health resources of the region are involved; that the leadership will be adequate for guidance and coordination; and that there is provision for continuous evaluation and planning.

The next focus is the effectiveness of the proposed cooperative arrangements. These arrangements must give evidence of serious commitment of the major health resources, assurances that the regional advisory group will have a continuing responsible role, and that the proposed activities will strengthen future cooperation.

Incidentally, the law requires that they must approve the operational grant before we can consider it.

If these two evaluations are favorable, the specific operational projects are reviewed. Each is judged for its own intrinsic merit, for its contribution to the cooperative arrangements, and for the degree to which it includes the core concept of the regional medical program.

Following this review, the National Advisory Council makes a judgment and recommends the amount of the grants to be awarded. Subsequently, staff of the Division discuss the conclusion of the total national review process with the applicant and others in the region. In this way, the results of the national review process and the re-

gional review process are brought together so that optimum utilization of Federal funds is assured and regional initiative and prerogatives for decisionmaking are protected and strengthened.

EXAMPLES OF PROJECTS

These initial applications for operational grants give us some insight into the types of projects that will be carried out in implementing regional medical programs. We recognize that each region will need to develop its own approach to strengthening its capabilities. However, the following examples may be useful in illustrating the types of projects that many regions are likely to consider:

(1) The exchange of personnel between medical schools and medical centers and community hospitals.

(2) Continuing education programs for medical practitioners and allied health workers, at both local facilities and medical centers.

(3) Provision of consultation and other assistance to practicing physicians by medical center and other specialized personnel.

(4) Development of learning centers at community hospitals.

(5) Demonstrations of coronary care in teaching and community hospitals.

(6) Expansion of cerebral vascular diagnostic resources.

(7) Linking of rural hospitals with a medical center to provide an automated electro-cardiography analysis system.

(8) Demonstrations of improved methods of utilizing computers in monitoring physiologic data and in providing data for the use of practicing physicians and hospitals.

(9) Studies of the best methods of providing selected detection, diagnostic and treatment services.

(10) Improvement of communication system and facilities joining medical centers and community hospitals.

(11) Development of information programs to establish communications, understanding, and cooperation among the institutions, organizations and individuals involved in the program.

INTERMOUNTAIN REGIONAL MEDICAL PROGRAM

The initial operational activities of the Intermountain regional medical program will make the following opportunities to medical practitioners in this region, which encompasses Utah and parts of Wyoming, Nevada and Idaho.

He will have available at his community hospital a communication network, including radio and television facilities, which will provide education programs and opportunities for interchange and discussion with consultants at the medical center.

He will have available at his community hospital for himself, nurses and other personnel, a training program in the resuscitation of patients with heart disease and the necessary equipment to make it possible to carry out these techniques. He will also have on call a medical consultant who has specially trained to head hospital cardiopulmonary arrest alert programs.

He will be able to attend training courses in the intensive care of heart patients or will have available for consultation medical and nursing specialists who have completed such training.

He may have tested at his hospital the feasibility of a system that transmits, in a 24-hour-day operation, physiological information on heart disease patients to a computer facility in Salt Lake City and transmits promptly back to stations within his hospital information for diagnosis and treatment.

He will have available at his hospital a medical consultant who is a source of special information and advice on cancer as well as more up-to-date information on the occurrence and care of cancer from a coordinated tumor registry and more specialized techniques for handling pathologic specimens.

Consultants may visit his hospital (if it is in a community with less than 10,000 persons) periodically, to assist in the diagnosis and care of heart disease patients.

He may apply for a special clinical traineeship in cardiology that will involve specialized training at five cooperating medical institutions.

He will have available, a communication and information exchange service that will provide information on the prevention and control of these diseases to public groups as well as to professional and allied health workers.

FUTURE OF PROGRAM

It is anticipated that in 1968 operational programs will begin in more than half of the regions. It is vital that this new program be supported adequately as it moves from the support of planning activities to the establishment of operational programs. Planning activities are underway throughout the Nation. They have evoked great enthusiasm and they show great promise. The increased funds requested for the fiscal year 1968 will be used largely to turn the plans into action. Although planning activities will continue, the emphasis will be shifted to the implementation of operational pilot projects. Grants to support the operational phase of the program will require much larger sums of money than the planning activities.

Regional medical programs will not compete with programs administered elsewhere in the Public Health Service. Applicants must demonstrate the relation of support requested under this program to funds and support available from other Federal and non-Federal sources.

In summary the grant funds requested will be utilized for (1) initial funding of the remaining few planning grant applications which will not be approved by July 1, 1967; (2) second-year funding for previously approved planning grant applications; and (3) to initiate new operational programs in more than half of the regions. It is expected that the greatest proportion of these funds will be utilized for operational programs.

The appropriation request for the Division of Regional Medical Programs totals $64,314,000. It includes $59,400,000 for grants, which, when combined with $21 million carried forward from the current year provides a total of $80,400,000 in grant funds. This is an increase of $48,448,000 over the estimated 1967 obligations. The request for direct operations includes an increase of $2,355,000 for professional and technical assistance, of which $2,225,000 is for contracts; there is also an increase of $93,000 for review and approval of grants, and

$118,000 for program direction. This request will allow a total increase of 14 positions over the 1967 operating level.

Mr. FLOOD. What you have just said in the last few minutes is what I meant from the very first day. That is what I understood and what I hoped for and believed in and was enthused about. Now you have me enthused again. I am taking another bite at that fly.

SUMMARY OF BUDGET REQUEST FOR REGIONAL PROGRAMS

Your appropriation for 1967 was $45,004,000—I am always curious how you get these stray thousands—and your request for 1968 is $64,314,000. That is an increase of $19,310,000, but you have found carryovers here, you have adjustments. You estimate you will actually obligate $34,300,000 during the current year and $85,314,000 in 1968. That is what you think you will actually obligate?

Dr. MARSTON. Yes, sir.

LAPSE OF APPROPRIATIONS

Mr. FLOOD. How do you explain the fact you have $12 million of appropriated funds that lapsed?

Dr. MARSTON. We had applications in hand that exceeded the total authorization for last year. On the other hand, it was very important in the early stages of the program to have a thorough evaluation of each application that came in and we made the deliberate decision this should take precedence.

Mr. FLOOD. As of December 31 last year?

Dr. MARSTON. Yes. There was another complication. There had been a request for a 2-year authorization which was decreased to 1½ years. It is our view that if we had had the full 2-year authorization these funds would not have lapsed.

Mr. FLOOD. Most of the increase would be used to put into actual operation projects that are now in the planning stage?

Dr. MARSTON. Yes, sir.

STATUS OF REGIONAL MEDICAL PROGRAMS

Mr. FLOOD. Will you place in the record a list of the regions and the status of each one and indicate those now in the planning stage?

(The information follows:)

Status of regional medical programs (as of Apr. 18, 1967)

Region [1]	Planning grant under review	Planning grant awarded	Operational grant awarded
Alabama		X	
Albany (N.Y.)		X	X
Arizona		X	
Arkansas	X		
Bi-State (St. Louis, Mo., and southern Illinois)		X	
California		X	
Central New York		X	
Central Ohio		X	
Colorado-Wyoming		X	
Connecticut		X	
Delaware Valley		X	
Florida	X		
Georgia		X	
Hawaii		X	
Illinois	X		
Indiana		X	
Intermountain (Utah, and portions of surrounding States)		X	X
Iowa		X	
Kansas		X	X
Louisiana		X	
Maine	X		
Maryland		X	
Memphis (Tenn.)		X	
Metropolitan Washington, D.C		X	
Michigan	X		
Mississippi	X		
Missouri		X	X
Mountain States (Idaho, Montana, Nevada, and Wyoming)		X	
Nebraska-South Dakota		X	
New Jersey	X		
New Mexico		X	
New York City	X		
North Carolina		X	
North Dakota	X		
Northern New England		X	
Northlands (Minnesota)		X	
Ohio Valley		X	
Oklahoma		X	
Oregon	X		
Rochester (N.Y.)		X	
South Carolina		X	
Susquehanna Valley	X		
Tennessee (mid-South)		X	
Texas		X	
Tri-State (Massachusetts, Rhode Island, and New Hampshire)	X		
Virginia		X	
Washington-Alaska		X	
West Virginia		X	
Western New York		X	
Western Pennsylvania		X	
Wisconsin		X	

[1] Preliminary regions have been defined for planning purposes on the original applications; State designations do not indicate they are conterminous with State lines. These preliminary regions may be modified on the basis of experience.

ESTIMATED NEW OPERATIONAL GRANTS

Mr. FLOOD. We would like to know how many will change to operations and what will be the date.

Dr. SHANNON. Can this be put as an estimate, because it will appear in the public record?

Dr. MARSTON. If we could just use numbers and not names.

Dr. SHANNON. I think the chairman would like the names.

Mr. FLOOD. Yes; let us have the names.

(The information follows:)

New operational grants for regional medical programs expected to be awarded in fiscal year 1968

Region [1]	Effective starting date of planning grant	Estimated starting date of operational grant [2]
Alabama	Jan. 1, 1967	Apr. 1, 1968
California	Nov. 1, 1966	May 1, 1968
Central New York	Jan. 1, 1967	Apr. 1, 1968
Colorado-Wyoming	do	Do.
Connecticut	July 1, 1966	Jan. 1, 1968
Georgia	Jan. 1, 1967	Apr. 1, 1968
Hawaii	July 1, 1966	Jan. 1, 1968
Indiana	Jan. 1, 1967	Apr. 1, 1968
Iowa	Dec. 1, 1966	Mar. 1, 1968
Louisiana	Jan. 1, 1967	Apr. 1, 1968
Maryland	do	Do.
Metropolitan Washington	do	Do.
Mountain States	Nov. 1, 1966	May. 1, 1968
Nebraska-South Dakota	Jan. 1, 1967	Apr. 1, 1968
New Mexico	Oct. 1, 1966	Jan. 1, 1968
North Carolina	July 1, 1966	Oct. 1, 1967
Northern New England	do	Do.
Northlands	Jan. 1, 1967	Apr. 1, 1968
Ohio Valley	do	Do.
Oklahoma	Sept. 1, 1966	Dec. 1, 1967
Rochester, N. Y	Oct. 1, 1966	Jan. 1, 1968
South Carolina	Jan. 1, 1967	Apr. 1, 1968
Tennessee Mid-South	July 1, 1966	Oct. 1, 1967
Texas	do	Jan. 1, 1968
Virginia	Jan. 1, 1967	Apr. 1, 1968
Washington-Alaska	Sept. 1, 1966	Jan. 1, 1968
West Virginia	Jan. 1, 1967	Apr. 1, 1968
Western New York	Dec. 1, 1966	Mar. 1, 1968
Western Pennsylvania	Jan. 1, 1967	Apr. 1, 1968
Wisconsin	Sept. 1, 1966	Jan. 1, 1968

[1] Preliminary regions have been defined for planning purposes on the original applications; State designations do not indicate they are conterminous with State lines. These preliminary regions may be modified on the basis of experience.

[2] Estimated dates are based on the assumption that the first operational grant to a region will be made approximately 15 to 18 months after the effective date of the planning grant.

SPECIAL REPORT ON PROGRAM DEVELOPMENTS

Mr. FLOOD. We will also place in the record your special report on the program.

(The report follows:)

SPECIAL REPORT: DEVELOPMENTS IN REGIONAL MEDICAL PROGRAMS

PREFACE

On October 6, 1965, Public Law 89–239, the Heart Disease, Cancer, and Stroke Amendments of 1965—which became Title IX of the Public Health Service Act—launched, in this country, a new departure in health care: authorization of grants to assist in the planning and establishment of regional medical programs throughout the country to combat heart disease, cancer, stroke, and related diseases in areas to be identified and designated on the regional level by the people themselves.

The philosophy, hopes and fears that accompanied the development and ultimate passage of that legislation have now been replaced by identifiable progress, and the recognition of problems for which solutions will mean continuing progress toward fulfilling the purpose of the law. This Report presents a briefing to this point in time of the developments of this new program.

OBJECTIVE OF THE REGIONAL MEDICAL PROGRAMS

The Regional Medical Programs seeks to assist the Nation's health institutions and professions in capitalizing on the rapid advances of scientific medicine in the prevention, diagnosis, treatment, and rehabilitation of patients with heart disease, cancer, stroke or related diseases. The authorizing legislation asserts

the grants are to assist in establishing regional cooperative arrangements among medical schools, research institutes, hospitals and other health institutions and agencies so that the health professions and their medical institutions will have available the latest advances in diagnosing and treating these diseases. Grant funds will support cooperative arrangements for research, training (including continuing medical education), improvement of patient care as well as the health manpower and health facilities of the Nation. The law also states that these purposes should be accomplished without interfering with the patterns of professional practice or hospital administration.

Shifting responsibility for initiative from the Federal to the regional level, this program emphasizes the application of new knoweldge and skills to community needs. It stresses the strengthening and expansion of established cooperative arrangements and the establishment and development of new ones among existing health institutions and organizations at the regional level to provide the mechanism for linking the individuals and institutions involved in research and teaching to their colleagues in community practice and their institutions. Utilizing individual review rather than pat formula, the mechanism will prevent dominance of a Regional Program by any one institution or group.

This law represents a vote of confidence in the willingness and ability of regional groups to accept the basic responsibility for devising their own Regional Programs to accomplish the purposes of the law. The flexibility of the legislative provisions emphasize that regional groups are to develop their own programs to meet their own needs. To maintain this flexibility, no master blueprints were called for, to structure Regional Medical Programs either in the rural or the metropolitan areas—for indeed, there are no blueprints, only an acute awareness of the complexities and wide differences across the nation.

A YEAR'S EXPERIENCE

After just one year of experience, considerable evidence is coming to light which seems to justify this law's almost naive trust and faith in the ability of formerly divergent medical and health interests to cooperate on a voluntary basis in accomplishing important health objectives. This experience divides into four phases.

EXPERIENCE—PHASE I

The first, from the signing of the legislation in October, 1965 until about February of 1966, was devoted to reassuring various medical practitioners and groups that the Programs were not intended to divert patients to distant medical centers with no concern for the local practicing physicians or their community hospitals. Some medical school people had to be reassured that their educational, research, and clinical care institutions were not being asked to assume total responsibiilty for the medical care for their regions in the fields of heart disease, cancer, and stroke. Nonaffiliated hospitals and all other public and private health organizations had to be told that they would have a role to play in the Program.

During this period meetings were held in regions throughout the country to discuss implementation of programs. The Regional Medical Programs appeared as a topic for discussion on the programs of many major medical professional organizations. In December of 1965 the Division of Regional Medical Programs was established within the National Institutes of Health—whose staff had been contacted by literally hundreds of medical organizations and groups expressing interest and support—and the new National Advisory Council of the Division held its first meeting. The administrative decision to locate this new responsibility of the Public Health Service within the NIH organization—made prior to the signing of the legislation—emphasized that the Regional Medical Programs concept focused on the relationship and interaction between the development of new scientific knowledge and better medical care.

EXPERIENCE—PHASE II

The next phase lasted from February into April of 1966. Special groups expert in such related fields as continuing education, community health planning, and hospital administration gave advice on implementation. Regulations were drafted, and application forms were developed and widely distributed. A National Advisory Council meeting devised a process for the review of applications that consisted of preliminary review by staff and by a group of *ad hoc* consultants

prior to the review for decision by the National Advisory Council as required by the law. Council members and consultants interpreted the program throughout the country in speeches, in their own professional organizations, and in the development of individual regional plans in their own areas.

EXPERIENCE—PHASE III

During the next phase (April until June of 1966), the emphasis changed from reassurance, definition, establishment of policy and preparation of materials to the receipt and review of applications for planning grants. No deadlines for the receipt of the first applications were announced. Instead, frequent meetings of the *ad hoc* initial review groups were held so that applications could be considered without undue delay and without a crash program. These review groups, representing a variety of backgrounds in health affairs, were able to consider and reach a consensus on the merits of applications with varying approaches to the planning of a Regional Medical Program. After these review meetings, the National Advisory Council met to consider these first applications in April, June, and August.

Between April and June, a total of 39 planning grant applications were received. In reviewing the first applications, certain areas of emphasis and problems were identifiable which were then reflected in the Division's organization and policy development. An example of emphasis was the recognition given to continuing education as a major function of Regional Medical Programs. On the other hand, an example of a problem was the large-scale proposals for systems analysis included in the application for the planning of Regional Medical Programs. The Guidelines which were under development during this period took these and other matters into consideration in the development of Division policy. As a result, the Guidelines document issued on July 1 was based not only on the intent of the Congress, the judgment of the National Advisory Council members and other consultants, but also on experience in the actual review of planning grant applications.

EXPERIENCE—PHASE IV

The fourth phase of the first year of the program, lasting from June until October, was concerned with the continued review of applications for planning grants; a rapid buildup of activities in continuing education; preparation for the required Report to Congress in June 1967 including initial plans for a National Conference to provide representative groups from the active and proposed regions the opportunity to provide their grass-roots input for the Report; and anticipation of applications for operational grants.

In considering the applications, the Council found that a straight "yes" or "no" answer was seldom sufficient to communicate its intent in making recommendations. One of the results of this was the request by the Council that the staff of the Division discuss their action with the applicant, review the reasons for that action, and obtain additional information or clarification concerning points made by the Council. It was the Council's opinion that this interchange between the applicant group and the staff of the Division would improve bilateral understanding of the proposal. When the additional information requested would not affect the basic soundness of the proposal, the Council recommended approval conditional upon receipt of clarifying information by the staff. Where the information to be provided was more substantial, the Council deferred action on the application until it could consider the additional information supplied by the applicant. On other applications, the Council did not feel that it could recommend approval of the application until substantial revisions had been made in the proposal. In recommending revision, the Council made clear that it hoped and expected to see the revised application at the next meeting. However, it also made it clear that it was asking the staff not to require conformity of applications to a standard pattern in negotiating the required revisions. The Council wanted to see these applications retain their unique characteristics as proposals from the region, but they felt a strong sense of responsibility that the award of Federal grant funds could only be recommended after satisfactory evidence that the proposal, whatever its proposed approach, could reasonably be expected to result in a plan for a Regional Medical Program that accomplished the objectives of the legislation.

PROGRESS OF REGIONAL MEDICAL PROGRAMS

One of the most productive sources of information during this first year of the program has been the grant applications themselves. They provide preliminary

insights into the types of activities to be carried out in developing Regional Medical Programs as well as a rough gauge of the extent to which "regional cooperative arrangements" among medical schools, research institutions, hospitals, and other health agencies and institutions have developed to date.

As of December 31, 1966, 34 approved planning grants had been funded. (Exhibit A) Fourteen other applications are in the process of being reviewed. The 48 applications approved or under review include, in the aggregate, regions in which over 90 percent of the Nation's population reside.

The review process is now in the hands of a duly appointed Review Committee (Exhibit B) which conveys its recommendations to the National Advisory Council (Exhibit C). That group, in turn, reviews and recommends action on grants to the Surgeon General.

The initial planning activities for most Regional Medical Programs have four major areas of acitivity in common:

(1) Organization and staffing;

(2) Studies to collect and analyze data on resources and needs;

(3) Development of activities to strengthen communications, exchange of ideas and information, and relationships among the health organization and groups of the region; and

(4) Preparation of specific proposals for operational projects, including the initiation of any feasibility studies which may be undertaken as part of the initial planning.

ORGANIZATION AND STAFFING

Major health groups throughout the country—using a variety of approaches—have cooperated in the development of regional medical programs. Participating organizations must agree upon the institution that is to assume responsibility for coordinating the development of the program. As in other aspects of the law provision is made for flexibility in this respect.

Of the 48 cases of which applications have been approved or are under consideration; this responsibility has been assumed by 29 medical schools, 14 nonprofit agencies, of which 12 were agencies newly established for this purpose, one governmental health agency; and in 4 cases, a medical society or related health foundation.

In addition, over 600 other health, government and civic institutions and agencies have been identified in the applications as participants in the initial planning. Hospitals represent a large majority of this number. Among the other key participants are the medical societies and official state or local health agencies. Most applications indicate the intention to expand the network of participating organizations during the planning process.

The membership of Regional Advisory Groups is an index of the nature and scope of the developing cooperative arrangements. In line with the intent of Section 903(b) of Public Law 89-239, there has been widespread participation in this group. On an overall basis, the membership is distributed in the following fashion in the applications approved and under consideration:

Categories	Number	Percentage
Practicing physicians	279	20.8
Medical school-medical center representatives	242	18.1
Hospital administrators	163	12.1
Voluntary health agency officials	169	12.6
Public health officials	114	8.4
Other health workers	111	8.3
Members of the consumer public	189	14.0
Other	76	5.7
Total	1,343	100.0

Since shortages of medical administrators and planners present difficulties in staffing, many programs are looking to a variety of specialties for assistance, including statistics, sociology, economics, and education. In addition, there is a growing trend to seek advice and assistance from university staffs and private firms in such areas as computer technology, operations research and systems analysis.

INVENTORY STUDIES

The second major aspect of Regional Medical Programs planning is the conduct of studies on resources, needs, and problems relating to both. The most frequent surveys mentioned are concerned with the collection of data on health manpower and facilities and their specialized capabilities. Almost all applications propose studies of the distribution of and needs for medical and nursing manpower. Most applications also give high priority to problems associated with shortages of laboratory technicians and other categories of supporting health manpower.

Other principal areas in which studies are being conducted concern the incidence and prevalence of heart disease, cancer and stroke and the availability of and needs for training adequate resources of people to provide the best possible diagnosis and treatment of such patients.

Needs for and studies to determine attitudes about continuing education activities also receive major attention in these planning efforts and high priority is being given to the needs of not only physicians, but other allied health personnel including dentists and nurses.

The determination of the appropriate area and scope of regional responsibilities and the nature of inter-regional relationships are receiving major attention during the planning process in almost all regions. It is recognized that the preliminary planning regions may undergo many changes during and subsequent to the planning phase. The planning studies and other activities are expected to provide data and experiences for such modifications.

STRENGTHENING INTER-AGENCY RELATIONSHIPS

The strengthening of communications and inter-relationships among the existing and prospective participtaing organizations is an important part of the initial planning in all programs. A variety of approaches are being considered and tested to facilitate linkages among the various participants. The most commonly reported techniques are the employment of liaison personnel; the organization of task forces; the conduct of workshops and conferences; and the development of joint operational programs.

In many regions, continuing committees to supplement the official Regional Advisory Groups are being established. In some cases, these groups are organized by areas of common interest and in others on a functional or a geographical basis. These organizational instruments are considered important ways of maintaining and furthering communication, understanding, and participation.

PROPOSALS FOR OPERATIONAL PROJECTS

The fourth major aspect of planning activities in each of the regions is the development of proposals for the "pilot projects" that will initiate the operational phase of the Regional Medical Programs. This is a principal purpose of the planning activity which is of necessity, directed toward the subsequent operational phase. Although they may enter the operational phase at any time, it is expected that further planning based on continuing evaluation will continue throughout the life of the Regional Program. By the same token, pilot projects may be undertaken in portions of the Program for which initial planning has been completed.

THE CURRENT PHASE—OPERATIONAL PROGRAMS

Since October 1966, a major proportion of the Division's attention has been devoted to the development of the appropriate processes for review and approval of operational grant applications stemming from the planning process. As of December 31, 1966, four applications for operational Programs have been received and are under review.

Because these operational proposals represent the beginning of activities which will continue to evolve and expand, the review processes involves an important relationship among the Division's staff, the Review Committee, the National Advisory Council, and the applicants. The frequent meetings of both the Review Committee and the National Advisory Council, as well as the extensive staff negotiations with applicants, through the Division's Development and Assistance Branch represent beginnings in the developments of these relationships.

The review process for these new types of applications has also required flexible but specific involvement of Federal and other sources of support. Just as this program calls for an integrating and synthesizing activity on the regional level, so the Division also has a synthesizing and integrating responsibility at the national level.

The concept of the review and approval process developed for planning applications must continue to recognize the importance of the decision-making process carried out in the individual regions as they apply to the operational grant proposals. The establishment of this decision-making mechanism on the local level, a primary goal of this law, is necessary since different priorities exist in different parts of the country. On the other hand, neither the National Advisory Council nor the Public Health Service can delegate their basic responsibility and accountability that Federal funds will be expended wisely.

After operational grant applications have been received and reviewed by the initial Review Committee, additional information is gained by site visits. In many instances these are carried out by combined Committee-Council teams. There is then a recommendation by the National Advisory Council and the final action involving administrative decisions by the Public Health Service. In addition to this relatively standard process, the staff must tailor other activities in the review process to meet the particular needs of individual applications. In many instances this involves getting additional information on scientific merit or other aspects from other Institutes or Bureaus of the Public Health Service, or other agencies in the government, to assure that acceptable standards are maintained and to explore the other potentialities for support.

There is a need to develop criteria for choosing among an array of meritorious operational projects. The scope and flexibility of the law is such that there is no difficulty in viewing a great number of worthwhile and needed projects as being eligible for support. However, criteria such as the following are being used to set priorities:

The degree to which the project would assist in the wise utilization of manpower.

The degree to which proposed projects involved multiple institutions and different types of institutions there by providing more effective development of cooperative arrangements, particularly in the initial steps.

The degree to which the proposed project provides for strengthening the relationship of scientific knowledge to medical service.

The degree to which the project will contribute to the basic goal of continuing education and training.

The degree to which unique regional resources or talent might be utilized more effectively.

The degree to which the proposed project represents a critical focus which, if supported, will effectively benefit a larger series of projects and programs.

The degree to which the project offers the opportunity to support gap areas and new and innovative approaches.

The Regional Medical Programs proceeding into the operational phase are advised to select those activities they can see clearly, rather than depending on the development of some master plan or projects in vague and unexplored areas. Since these initial steps have usually built on existing strengths, they provide the basis for furthering cooperative relationships and refinement of the essential decision-making process at the regional level.

EXHIBIT A

Planning grants for regional medical programs approved and funded as of Dec. 31, 1966

Regional designation	Preliminary planning region	Population estimated 1965 [1]	Coordinating headquarters	Program coordinator	Effecting starting date	Period of grant (years)	1st year award
Alabama	Alabama	3,500,000	University of Alabama Medical Center.	Joceph F. Volker, D.D.S., vice president for health affairs, University of Alabama Medical Center, Birmingham, Ala.	Jan. 1, 1967	2½	$318,046
Albany, N.Y.	Northeastern New York, southern Vermont, and western Massachusetts.	1,900,000	Albany Medical College of Union University at Albany Medical Center.	Frank M. Woolsey, Jr., M.D., associate dean and professor and chairman, Department of Postgraduate Medicine, Albany Medical College, Albany, N.Y.	July 1, 1966	3	373,254
California	California	18,600,000	California Committee on Regional Medical Programs.	Nemat O. Borhani, M.D., chief, Bureau of Chronic Disease, California State Department of Public Health, Berkeley, Calif.	Nov. 1, 1966	3	223,400
Central New York	Syracuse, N.Y., and 15 surrounding counties.	1,800,000	Upstate Medical Center, State University of New York at Syracuse.	Richard H. Lyons, M.D., professor and chairman, Department of Medicine, State University of New York Upstate Medical Center, Syracuse, N.Y.	Jan. 1, 1967	2	289,522
Colorado-Wyoming	Colorado and Wyoming	2,300,000	University of Colorado Medical Center.	C. Wesley Eisele, M.D., associate dean for postgraduate medical education, University of Colorado, Denver, Colo.	do	2½	284,678
Connecticut	Connecticut	2,800,000	Yale University School of Medicine and University of Connecticut School of Medicine.	Henry T. Clark, Jr., M.D., New Haven, Conn.	July 1, 1966	2	406,622
Georgia	Georgia	4,400,000	Medical Association of Georgia.	J. W. Chambers, M.D., coordinator for Georgia regional medical programs, Medical Association of Georgia, Atlanta, Ga.	Jan. 1, 1967	2½	240,098
Hawaii	Hawaii	800,000	University of Hawaii College of Health Sciences.	Windsor C. Cutting, M.D., dean, College of Health Sciences, Honolulu, Hawaii.	July 1, 1966	2	108,006
Indiana	Indiana	4,900,000	Indiana University School of Medicine.	George T. Lukemeyer, M.D., associate dean, Indiana University School of Medicine, Indiana University Medical Center, Indianapolis, Ind.	Jan. 1, 1967	2½	384,750

Intermountain	Utah and portions of Wyoming, Montana, Idaho, and Nevada.	2,200,000	University of Utah School of Medicine.	C. Hilmon Castle, M.D., associate dean and chairman, Department of Postgraduate Education, University of Utah, Salt Lake City, Utah.	July 1,1966	3	456,415
Iowa	Iowa	2,760,000	University of Iowa College of medicine.	Robert C. Hardin, M.D., dean, University of Iowa, College of Medicine, Iowa City, Iowa.	Dec. 1,1966 Dec.	2	291,348
Kansas	Kansas	2,200,000	University of Kansas Medical Center.	Russell C. Mills, Ph. D., associate dean, University of Kansas, Kansas City, Kans.	July 1,1966	2	197,945
Louisiana	Louisiana	3,500,000	Louisiana State Department of Hospitals.	E. Lee Agerton, director, Louisiana State Department of Hospitals, Baton Rouge, La.	Jan. 1,1967	2	490,448
Maryland	Maryland	3,520,000	Steering Committee of the Regional Medical Program for Maryland.	William J. Peeples, M.D., commissioner, Maryland State Department of Health, Baltimore, Md.	do	2	518,443
Metropolitan Washington, D.C.	District of Columbia and contiguous counties of Maryland (2) and Virginia (2).	2,050,000	District of Columbia Medical Society.	Thomas W. Mattingly, M.D., District of Columbia Medical Society, Washington, D.C.	do	2	203,790
Missouri	Missouri	4,500,000	University of Missouri School of Medicine.	Vernon E. Wilson, M.D., dean, School of Medicine, University of Missouri, Columbia, Mo.	July 1,1966	3	398,556
Nebraska-South Dakota	Nebraska and South Dakota.	2,200,000	Nebraska State Medical Association.	Henry M. Lemon, M.D., director, Eppley Cancer Institute, professor of medicine, University of Nebraska College of Medicine, Omaha, Nebr.	Jan. 1,1967	2	289,350
New Mexico	New Mexico	1,000,000	University of New Mexico School of Medicine.	Reginald Fitz, M.D., dean, University of New Mexico School of Medicine, Albuquerque, N. Mex.	Oct. 1,1966	3	384,317
North Carolina	North Carolina	4,900,000	Association for Regional Medical Programs in North Carolina.	Harvey L. Smith, Ph. D., director, Social Research Section, professor of sociology, University of North Carolina, Chapel Hill, N.C.	July 1,1966 Jan. 1,1967	2 ½	287,266 [2] 148,585
Northern New England	Vermont and 3 counties in northeast New York.	550,000	University of Vermont School of Medicine.	Robert W. Coon, M.D., professor and Chairman, Department of Pathology, University of Vermont Medical School, Burlington, Vt.	July 1,1966	3	294,770
Northlands	Minnesota	3,600,000	Minnesota State Foundation	J. Minnott Stickney, M.D., Minnesota State Medical Association, Rochester, Minn.	Jan. 1,1967	2½	370,904
Ohio Valley	Greater part of Kentucky and contiguous parts of Ohio, Indiana, and West Virginia which comprise the Ohio Valley.	5,900,000	Ohio Valley Regional Medical Program.	William H. McBeath, M.D., director, Ohio Valley regional medical program, Lexington, Ky.	do	2	346,760
Oklahoma	Oklahoma	2,500,000	University of Oklahoma Medical Center.	Ben I. Heller, M.D., University of Oklahoma Medical Center, Oklahoma City, Okla.	Sept. 1,1966	2	177,963

Footnotes at the end of table.

Planning grants for regional medical programs approved and funded as of Dec. 31, 1966—Continued

Regional designation	Preliminary planning region	Population estimated 1965 [1]	Coordinating headquarters	Program coordinator	Effecting starting date	Period of grant (years)	1st year award
Rochester, N.Y.	Rochester, N.Y., and 11 surrounding counties.	1,200,000	University of Rochester School of Medicine and Dentistry.	Ralph C. Parker, Jr., M.D., clinical associate professor of medicine, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.	Oct. 1, 1966	3	$306,985
South Carolina	South Carolina	2,500,000	Medical College of South Carolina.	Charles P. Summerall III, M.D., association in medicine (cardiology), Department of Medicine, Medical College Hospital, Charleston, S.C.	Jan. 1, 1967	1	65,906
Tennessee, Midsouth	Eastern and central Tennessee and contiguous parts of southern Kentucky and northern Alabama.	2,600,000	Vanderbilt University School of Medicine and Meharry College of Medicine.	Randolph Batson, M.D., dean and director of medical affairs, Vanderbilt University, Nashville, Tenn.	July 1, 1966	2	265,841
Texas	Texas	10,500,000	University of Texas	Charles A. LeMaistre, M.D., vice-chancellor for health affairs, University of Texas, Austin, Tex.	do	3	1,271,013
Virginia	Virginia	4,500,000	Medical College of Virginia and University of Virginia School of Medicine.	Charles L. Crockett, Jr., M.D., assistant dean, University of Virginia, University of Virginia Hospital, Charlottesville, Va.	Jan. 1, 1967	2	237,800
Washington-Alaska	Washington and Alaska	3,200,000	University of Washington School of Medicine.	Donal R. Sparkman, M.D., associate professor of medicine, University of Washington School of Medicine, Seattle, Wash.	Sept. 1, 1966	3	266,248
West Virginia	West Virginia	1,800,000	West Virginia University Medical Center.	Clark K. Sleeth, M.D., dean, West Virginia University, School of Medicine, West Virginia University Medical Center, Morgantown, W. Va.	Jan. 1, 1967	2½	150,798
Western interstate	Idaho, Montana, Nevada, and Wyoming.	2,200,000	Western Interstate Commission for Higher Education.	Kevin P. Bunnell, Ph. D., associate director, Western Interstate Comsion for Higher Education, Boulder, Colo.	Nov. 1, 1966	2	876,855
Western New York	Buffalo, N.Y., and 7 surrounding counties.	1,920,000	School of Medicine, State University of New York at Buffalo, in cooperation with the Health Organization of Western New York.	Douglas M. Surgenor, M.D., dean, School of Medicine, State University of New York at Buffalo, Buffalo, N.Y.	Dec. 1, 1966	2	149,241
Western Pennsylvania	Pittsburgh, Pa., and 28 surrounding counties.	4,200,000	University Health Center of Pittsburgh.	Francis S. Cheever, M.D., dean, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.	Jan. 1, 1967	2½	271,736
Wisconsin	Wisconsin	4,100,000	Wisconsin Regional Medical Programs, Inc.	John S. Hirschboeck, M.D., Wisconsin Regional Medical Programs, Inc., Milwaukee, Wis.	Sept. 1, 1966	2	344,418

[1] Includes some overlap of listed regions.

[2] Supplementary grant.

Exhibit B

Review Committee of Division of Regional Medical Programs

Mark Berke, Director, Mount Zion Hospital & Medical Center, San Francisco, California 94115.
Kevin P. Bunnell, Ed.D., Associate Director, Western Interstate Commission for Higher Education, Boulder, Colorado 80302.
Sidney B. Cohen, Management Consultant, Adelphi, Maryland 20783.
George James, M.D., Dean, Mt. Sinai School of Medicine, New York, New York, 10029.
Howard W. Kenney, M.D., Medical Director, John A. Andrew Memorial Hospital, Tuskegee, Alabama 36088.
Edward J. Kowalewski, M.D., Chairman, Board of Directors, American Academy of General Practice, Akron, Pennsylvania 17501.
George E. Miller, M.D., Director, Office of Research in Medical Education, College of Medicine, University of Illinois, Chicago, Illinois 60612.
Anne Pascasio, Ph.D., Oak Park Chateau, Oak Park, Illinois 60302.
David E. Rogers, M.D., Professor and Chairman, Department of Medicine, School of Medicine, Vanderbilt University, Nashville, Tennessee 37205.
C. H. William Ruhe, M.D., Assistant Secretary, Council on Medical Education, American Medical Association, Chicago, Illinois 60610.
Kerr L. White, M.D., Director, Division of Medical Care and Hospitals, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland 21205.

Exhibit C

National Advisory Council on Regional Medical Programs

Chairman: William H. Stewart, M.D., Surgeon General, U.S. Public Health Service, Bethesda, Maryland 20014.
Leonidas H. Berry, M.D., Professor, Cook County Graduate School of Medicine, and Senior Attending Physician, Michael Reese Hospital, Chicago, Illinois 60653.
Mary I. Bunting, Ph.D., President, Radcliffe College, Cambridge, Massachusetts 02138.
Michael E. DeBakey, M.D., Professor and Chairman, Department of Surgery, College of Medicine, Baylor University, Houston, Texas 77025.
Bruce W. Everist, M.D., Green Clinic, Ruston, Louisiana 71270.
John R. Hogness, M.D., Dean, School of Medicine, University of Washington, Seattle, Washington 98105.
James T. Howell, M.D., Executive Director, Henry Ford Hospital, Detroit, Michigan 48202.
Clark H. Millikan, M.D., Consultant in Neurology, Mayo Clinic, Rochester, Minnesota 55902.
George E. Moore, M.D., Director, Roswell Park Memorial Institute, Buffalo, New York 14203.
Edmund D. Pellegrino, M.D., Director of the Medical Center, State University of New York, Stony Brook, New York 11790.
Alfred M. Popma, M.D., Director, Department of Radiology, St. Luke's Hospital and School and Nursing, Boise, Idaho 83702.
Mack I. Shanholtz, M.D., State Health Commissioner, State Department of Health, Richmond, Virginia 23219.
Cornelius H. Traeger, M.D., 799 Park Avenue, New York, New York 10021.

IMMEDIATE PAST MEMBERS

Gordon R. Cumming, Administrator, Sacramento County Hospital, Sacramento, California 95817.
J. Willis Hurst, M.D., Professor and Chairman, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia 30333.
William J. Peeples, M.D., Commissioner of Health, State Office Building, Baltimore, Maryland 21201.
Robert J. Slater, M.D., Dean, College of Medicine, University of Vermont, Burlington, Vermont 05401.

EXHIBIT D

MEMBERS OF SPECIAL AD HOC ADVISORY COMMITTEE NAMED BY SURGEON GENERAL TO DEVELOP REPORT TO THE PRESIDENT AND THE CONGRESS DEALING WITH THE DIVISION OF REGIONAL MEDICAL PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH

Ray E. Brown, Director, Graduate Program in Hospital Administration, Duke University Medical Center, Durham, North Carolina.
*Michael E. DeBakey, M.D., Professor and Chairman, Department of Surgery, College of Medicine, Baylor University, Houston, Texas.
*Bruce W. Everist, M.D., Green Clinic, Ruston, Louisiana.
*James T. Howell, M.D., Executive Director, Henry Ford Hospital, Detroit, Michigan.
George James, M.D., Chairman, Department of Community Medicine, Mount Siani School of Medicine, New York, New York.
Boisfeuillet Jones, Director, Emily and Ernest Woodruff Foundation, Atlanta, Georgia.
Charles E. Odegaard, Ph. D., President, University of Washington, Seattle, Washington.
Edmund D. Pellegrino, M.D., Director, Medical Center, State University of New York, Stony Brook, New York.
Carl Henry William Rhue, M.D., American Medical Association, Chicago, Illinois.
Clark K. Sleeth, M.D., Dean, West Virginia University, School of Medicine, Morgantown, West Virginia.
Ray E. Trussell, M.D., Director, Columbia University School of Public Health and Administrative Medicine, New York, New York.
Burton Weisbrod, Ph. D., University of Wisconsin, Department of Economics, Madison, Wisconsin.
Robert E. Westlake, M.D., Medical Arts Building, Syracuse, New York.
Paul N. Ylvisaker, Ph. D., Vice President, Ford Foundation, New York, New York.

CONTRACT PROGRAMS

Mr. FLOOD. You want an increase of $2,225,000 to start two contract programs, one computer-base systems and another for continuing education of workers in the health professions. Tell us how much you have budgeted for each of 1968, and an estimate of cost for the following 4 years.

You can do that for the record.

(The information follows:)

Estimated level of project contracts, 1968–1972

[In thousands]

	1968	1969	1970	1971	1972
Continuing education of health professionals	$1,475	$1,600	$1,750	$1,900	$2,000
Operations research and systems analysis	750	900	1,100	1,600	1,800
Total	2,225	2,500	2,850	3,500	3,800

ADDITIONAL POSITIONS REQUESTED

Mr. FLOOD. You are requesting funds for 14 additional positions. How did you arrive at 14?

Dr. SHANNON. May I comment on those figures?

I have a conviction that, during the early stages of these operations, certain critical stages will be reached when it will be absolutely essen-

*Members of the National Advisory Council of Division of Regional Medical Programs.

tial to draw resources from a central pool to get them over a hump. I think that it is not unlikely that during the development of the program development we may well ask the Department for some freedom in our direct operation. This direct operation does not assume that we will, indeed, throw manpower into regions in critical areas in order to get them over the hump, nor have we calculated what the cost of that kind of operation would be. But I am convinced that some of the regions will turn to us for help, particularly in the early stages. So I would take these figures for personnel services and for operations as minimal figures. We probably will come before you for relaxation of the figures sometime during the year.

Mr. FLOOD. This would not surprise me.

Dr. MARSTON. This is very important.

Dr. SHANNON. This may make the difference between the region moving and not moving. We will not hesitate to bring it before you at a time when we can be much more specific in our budget.

REGIONAL PROGRAM IN PUERTO RICO

Mr. FLOOD. What about Puerto Rico? Dr. Arbona tried to sell this idea to me some years ago at a dinner. Do they not have a pretty advanced program of their own design down there? They have been trying to sell us this idea for years. Why do you want to change their program?

Dr. MARSTON. This is a very important point. First, Puerto Rico has not yet submitted an application for a planning grant. I visited them for many of the reasons you have brought out. Their interest in the regional medical programs under this law is the ability to do more than simply to have a relationship between structures, that is——

Mr. FLOOD. A relationship between structures?

Dr. MARSTON. Their concern in the medical school, in the new medical center they built, is not in the organization as much as it is the maintenance of the quality that can be related to the highly developed regional program that they have. There is a lot of enthusiasm for the regional medical program but they have a different problem than regions elsewhere in this country because they have a regionalization in Puerto Rico.

Mr. FLOOD. Is this program going to break up their system?

Dr. MARSTON. No, sir.

Dr. SHANNON. Puerto Rico has, as a framework, a system of seven or eight regional hospitals, that take care of the medical needs of a portion of Puerto Rico, together with a central referral system at the university. The problem they face is the distribution of their population. The service is of high quality in some areas and of low quality elsewhere. We want to export some of the excellence in the university environment to other areas. This they are not doing.

Dr. MARSTON. As well as they would like. And only a portion of their population is covered in this and it is the problem of relating this to the part of the practice of medicine carried on under private auspices. They look to this program to help in this area.

Mr. FLOOD. Thank you very much, gentlemen.

JUSTIFICATION MATERIAL

Regional Medical Programs

Amounts available for obligations

	1967	1968
Appropriation	$45,004,000	$64,314,000
Unobligated balance brought forward	21,934,000	21,000,000
Comparative transfers within NIH	356,000	
Unobligated balance carried forward	−21,000,000	
Unobligated balance lapsing Dec. 31, 1966	−11,982,000	
Total	34,312,000	85,314,000

Obligations by activities

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants: Regional medical programs		$31,952,000		$80,400,000		+$48,448,000
Direct operations:						
Professional and technical assistance	35	613,000	47	2,968,000	+12	+2,355,000
Review and approval of grants	48	723,000	49	816,000	+1	+93,000
Program direction	52	1,012,000	53	1,130,000	−1	+118,000
Total obligations	135	34,300,000	149	85,314,000	+14	+51,014,000
Unobligated balance, reserve		12,000				−12,000
Total, obligations and balance	135	34,312,000	149	85,314,000	+14	+51,002,000

Obligations by object

		1967 estimate	1968 estimate	Increase or decrease
	Total number of permanent positions	135	149	+14
	Full-time equivalent of other positions	2	4	+2
	Average number of all employees	128	142	+14
11	Personnel compensation:			
	Permanent positions	$1,186,000	$1,327,000	+$141,000
	Positions other than permanent	40,000	50,000	+10,000
	Other personnel compensation	12,000	23,000	+11,000
	Total personnel compensation	1,238,000	1,400,000	+162,000
12	Personnel benefits	103,000	115,000	+12,000
21	Travel and transportation of persons	90,000	120,000	+30,000
22	Transportation of things	2,000	2,000	
23	Rent, communications, and utilities	30,000	40,000	+10,000
24	Printing and reproduction	19,000	34,000	+15,000
25.1	Other services	371,000	396,000	+25,000
25.1	Project contracts		2,225,000	+2,225,000
	Payment to "National Institutes of Health management fund"	431,000	490,000	+59,000
26	Supplies and materials	14,000	23,000	+9,000
31	Equipment	50,000	69,000	+19,000
41	Grants, subsidies, and contributions	31,952,000	80,400,000	+48,448,000
	Total obligations by object	34,300,000	85,314,000	+51,014,000

Summary of changes

1967 enacted appropriation	$45,004,000
Unobligated balance brought forward to 1967	21,934,000
Comparative transfers within NIH	356,000
Unobligated balance carried forward to 1968	−21,000,000
Unobligated balance lapsing December 31, 1966	−11,982,000
Unobligated balance, reserve	−12,000
1967 estimated obligations	34,300,000
1968 estimated obligations	85,314,000
Total change	+51,014,000

	Base		Changes to base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in: 1. Annualization of positions new in 1967				$134,000
B. Program:				
1. Grants		$31,952,000		48,448,000
2. Professional and technical assistance	35	566,000	12	2,297,000
3. Review and approval of grants	48	658,000	1	41,000
4. Program direction	52	693,000	1	40,000
5. Centrally furnished services from the National Institutes of Health management fund:				
(a) Professional and technical assistance		47,000		21,000
(b) Review and approval of grants		65,000		6,000
(c) Program direction		319,000		32,000
Subtotal, management fund				59,000
Total, program items			14	50,885,000
DECREASES				
A. 1 less day of pay in 1968				−5,000
Total, net change requested			14	51,014,000

Explanation of Changes

Grants for regional medical programs.—The majority of regional medical programs will move from the planning stage to operational status during 1968. The increase of $48,448,000 will be used primarily to initiate these new operational programs and to provide second year funding to those programs begun in 1967. By the endof 1968, it is estimated that operational grants will have been awarded for pilot projects and demonstrations in some 48 regions.

Professional and technical assistance.—The program increase of 12 new positions and $2,297,000 will be used to provide assistance in the implementation of new regional medical programs, increase the supply of medical personnel trained in the concepts and methodologies of continuing education for physicians and other health service workers, and support controlled studies of the feasibility of utilizing computer-based systems effectively in regional medical programs.

Review and approval of grants.—The program increase of one position and $41,000 will provide support for increased workload and complexity in the review and management of operational grants.

Program direction.—An increase of one position and $40,000 will be used to increase the capability of the program direction staff in the area of computer-based systems and their application to regional medical programs.

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.

The Public Health Service Act, Title IX, Education, Research, Training, and Demonstrations in the Fields of Heart Disease, Cancer, Stroke and Related Diseases.

"SEC. 900. The purposes of this title are—

"(a) Through grants, to encourage and assist in the establishment of regional cooperative arrangements among medical schools, research institutions, and hospitals for research and training (including continuing education) and for related demonstrations of patient care in the fields of heart disease, cancer, stroke, and related diseases; . . ."

"SEC. 901. (a) There are authorized to be appropriated $50,000,000 for the fiscal year ending June 30, 1966, $90,000,000 for the fiscal year ending June 30, 1967, and $200,000,000 for the fiscal year ending June 30, 1968, for grants to assist public or nonprofit private universities, medical schools, research institutions, and other public or nonprofit private institutions and agencies in planning, in conducting feasibility studies, and in operating pilot projects for the establishment, of regional medical programs of research, training, and demonstration activities for carrying out the purposes of this title. Sums appropriated under this section for any fiscal year shall remain available for making such grants until the end of the fiscal year following the fiscal year for which the appropriation is made."

GRANTS FOR REGIONAL MEDICAL PROGRAMS

Grants for regional medical programs:	
1967 estimate	$31,952,000
1968 estimate	80,400,000
Increase or decrease	+48,448,000

INTRODUCTION

Grants are awarded to assist in the planning and establishment of regional cooperative arrangements among medical schools, research centers, hospitals, and other medical institutions and for demonstrations of patient care in the fields of heart disease, cancer, stroke and related diseases. These cooperative arrangements and demonstration programs will afford the health professions and institutions of the Nation an opportunity to make the latest advances in the diagnosis and treatment of these diseases more widely available, and to do so in ways that are particularly responsive to the problems and possibilities of their regional areas.

Program plans for 1967 and 1968

Two general types of grants are authorized by the enabling legislation—planning grants and operational grants. The large majority of grants awarded in FY 1967 will be of the former type, for this is the year in which the basic relationships, characteristics, and even geographic areas of most of the Nation's regional medical programs are being planned. It is important to realize that there is no well defined, textbook approach to planning and implementing a regional medical program. The most effective ways of applying new medical knowledge to improving health services will vary from area to area, and can only grow out of a broadly representative regional effort which relies primarily on the knowledge, initiative, and resourcefulness of the people who live and work there. By the end of 1967, it is estimated that some 54 planning grant applications will have been received, representing regions which in the aggregate cover virtually the entire country including Hawaii and Puerto Rico.

By January 1, 1967, four operational grant applications had also been received and were in the review process, and others are expected, but it will not be until 1968 that most regional medical programs move into the operational phase. Operational grants will of necessity be much larger than planning grants. In fact, prototype estimates and the early applications received indicate that a single regional program could effectively utilize as much as $5,000,000 a year in its early stages. Features of a regional medical program might well require new complex diagnostic and treatment equipment, the conduct of extensive continuing education programs for health professionals, and the utilization of communication and data processing facilities. Applicants will require reasonable assurance of the availability of adequate funds to justify major career and institutional commitments during the planning and early operational phases. The increase of $48,448,000 in obligational authority in 1968 will help fund these operational grants and provide the necessary assurance of the availability of support.

Many different types of pilot projects need to be assisted, but a strong emphasis on continuing education of health professionals will be common to all of them. They may include such programs as the support of specialized consultants visiting community hospitals on a periodic schedule, and the conduct of scheduled training programs in community facilities and at medical centers. Innovative methods of presenting information and carrying out training sessions will be tested in numerous settings to determine more effective methods of reaching and involving busy medical practitioners and other types of health workers. The broader use of such techniques as two-way communication systems and closed-circuit television will be evaluated on a selected basis.

No attempt is made to list the countless types and varieties of projects being considered by the planning groups throughout the Nation. The approaches and proposals are imaginative and innovative. Careful review of planning applications by local and national advisory groups have assured that funds are being effectively used to develop workable, cooperative arrangements among medical schools, research institutions and hospitals, and for developing novel approaches for the most rapid and useful application of research in the diagnosis and treatment of heart disease, cancer, and stroke and related diseases.

Professional and Technical Assistance

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	35	$324,000	47	$391,000	+12	+$67,000
Other expenses		289,000		2,577,000		+2,288,000
Total	35	613,000	47	2,968,000	+12	+2,355,000

Of the $2,355,000 increases requested, $2,225,000 will be used to support contract programs in two broad areas—(a) the utilization of computer-based systems in regional medical programs, and (b) continuing education of workers in the health professions.

(a) Regional medical program planning involves study of the interrelationships among the components of the health system rather than the functioning of its individual components. Many of the early planning applications have proposed the utilization of systems analysis approaches. As a stimulus to the effective use of systems analysis at the regional level, and to guard against duplicative effort, the Division will conduct studies which concentrate on basic regional medical problems of general applicability, as well as supporting specific limited studies tailored to the needs of one or more regions in the area of computer-oriented communications.

Rapid developments in adapting time-shared computers to the needs of medical research and patient care, resulting from computer research supported by the National Institutes of Health at Massachusetts General Hospital, have made regional computer centers technically feasible. This technical breakthrough promises the commercial availability of the necessary hardware and supporting program aids, and thus suggests applications in the regional medical programs for rapid interchange of patient medical information between these centers and the community hospitals and physicians. Such interchange promises quicker utilization of new knowledge derived from medical research and more rapid feedback of patient information to the medical centers. The Division will be involved in supporting tests for determining the feasibility of using commercially available, time-sharing computer service bureaus as solutions to the problem of intraregional communication of medical information.

(b) One of the areas important to the success of regional medical programs is that of continuing education in the health fields. If the "latest advances" in the diagnosis and treatment of heart, cancer, and stroke are to be made more readily available to the Nation, attempts must be made to communicate those advances to individuals in the health professions. The legislation assumes that such information is available in the medical schools, research institutions, and hospitals for research and training and that through continuing education it may be shared with all engaged in health care.

There are, however, shortages of medical educators conducting research into new and improved techniques of continuing education. There is need for more trained teachers to staff university medical schools and departments of continuing education and a marked expansion of continuing education is required at the community hospital level in each of the regions where medical programs are to be established.

To achieve an expansion of trained personnel in this field, the Division proposes to contract with existing departments of continuing education in the medical schools and with other nonprofit organizations for long and short-term programs of training in continuing education, by awarding fellowships and traineeships for one to three years, and by also mounting a series of short courses of from one to six weeks to upgrade the teaching qualifications of existing personnel in continuing education. These approaches are designed to produce an increased supply of trained teachers, upgrade the qualifications of existing teaching personnel, and improve techniques of continuing education for the health professions.

The balance of the program increase will support expanded field activities providing help to regional groups in developing planning and operating grant applications and implementing operational activities. In addition to maintaining a scientific overview of the ongoing programs, the staff will also have increasing responsibilities for providing a vital communication link among the various regional groups and the Division. This interchange of information will enable each group to benefit from the experiences and innovative solutions to problems from other areas.

Included in this net increase is $38,000 for annualization of positions new in 1967, offset by $1,000 for one less day of pay in 1968. There are also increases of $21,000 for centrally furnished services from the "National Institutes of Health Management Fund".

Review and Approval of Grants

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	48	$441,000	49	$495,000	+1	+$54,000
Other expenses		282,000		321,000		+39,000
Total	48	723,000	49	816,000	+1	+93,000

An increase of $93,000 and one position is requested to strengthen the review and approval and grants management activities as the number and dollar volume of grants increase. The forthcoming operational grants will be inherently more complex than the planning grants, requiring more perceptive analysis and management. Included in this net increase is $48,000 for annualization of positions new in 1967, offset by $2,000 for one less day of pay in 1968. There are also increases of $6,000 for centrally furnished services from the "National Institutes of Health management fund."

Program Direction

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	52	$576,000	53	$629,000	+1	+$53,000
Other expenses		436,000		501,000		+65,000
Total	52	1,012,000	53	1,130,000	+1	+118,000

An increase of $118,000 and one position will be used to provide program direction in the field of computer-based systems and their utilization in regional medical programs. Included in the net increase is $48,000 for annualization of positions new in 1967, offset by $2,000 for one less day of pay in 1968. There is also an increase of $32,000 for centrally furnished services from the "National Institutes of Health management fund".

Division of regional medical programs new positions requested in 1968

Activity	Grade	Annual salary
Professional and technical assistance:		
Director grade	CO-6	$11,840
Senior grade (2)	CO-5	20,556
Engineer	GS-14	15,106
Scientist (2)	GS-14	30,212
Public health program specialist	GS-14	15,106
Public health analyst	GS-11	9,221
Public health analyst	GS-9	7,696
Administrative assistant	GS-7	6,451
Secretary	GS-6	5,867
Clerk-stenographer	GS-5	5,331
Total number of positions (12)		127,386
Review and approval of grants: Grants management specialist	GS-12	10,927
Program direction: Systems analyst	GS-15	17,550
Total new positions, all activities (14)		155,863

MONDAY, APRIL 17, 1967.

NATIONAL INSTITUTE OF MENTAL HEALTH

WITNESSES

DR. STANLEY F. YOLLES, DIRECTOR
DR. BERTRAM S. BROWN, DEPUTY DIRECTOR
DR. SHERMAN N. KIEFFER, ASSISTANT DIRECTOR FOR PATIENT CARE
DR. PHILLIP L. SIROTKIN, ASSOCIATE DIRECTOR FOR PROGRAM COORDINATION
B. J. SADESKY, EXECUTIVE OFFICER
CAROL E. MILLER, JR., BUDGET OFFICER
DR. WILLIAM H. STEWART, SURGEON GENERAL
G. R. CLAGUE, ACTING CHIEF FINANCE OFFICER, PHS
JAMES B. CARDWELL, DEPUTY ASSISTANT SECRETARY, BUDGET

Mental Health Research and Services

Object classification

[In thousands of dollars]

		1966 actual	1967 estimate	1968 estimate
	PUBLIC HEALTH SERVICE			
	Personnel compensation:			
11.1	Permanent positions	16,336	19,311	21,201
11.3	Positions other than permanent	948	1,177	1,177
11.5	Other personnel compensation	326	427	427
	Total personnel compensation	17,610	20,915	22,805
12.0	Personnel benefits	1,744	2,120	2,251
21.0	Travel and transportation of persons	982	1,257	1,355
22.0	Transportation of things	139	150	183
23.0	Rent, communications, and utilities	726	964	1,115
24.0	Printing and reproduction	196	250	253
25.1	Other services	4,516	6,339	11,901
25.3	Payment to: "National Institutes of Health management fund"	6,646	6,284	6,926
26.0	Supplies and materials	1,770	2,007	2,092
31.0	Equipment	836	1,163	1,754
41.0	Grants, subsidies, and contributions	168,975	183,660	197,728
	Subtotal	204,140	225,109	248,363
95.0	Quarters and subsistence charges	−28	−29	−29
	Total obligations, Public Health Service	204,112	225,080	248,334
	ALLOCATION TO SAINT ELIZABETHS HOSPITAL			
	Personnel compensation:			
11.1	Permanent positions	86	88	88
11.5	Other personnel compensation	12	15	15
	Total personnel compensation	98	103	103
12.0	Personnel benefits	7	8	8
23.0	Rent, communications, and utilities	23	24	24
25.1	Other services	1	1	1
26.0	Supplies and materials	----------	2	2
	Total obligations, Saint Elizabeths Hospital	129	138	138
99.0	Total obligations	204,241	225,218	248,472

Personnel summary

	1966 actual	1967 estimate	1968 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	2,285	2,494	2,744
Full-time equivalent of other positions	153	194	194
Average number of all employees	2,228	2,458	2,666
Average GS grade	7.2	7.4	7.6
Average GS salary	$7,605	$8,313	$8,429
ALLOCATION TO SAINT ELIZABETHS HOSPITAL			
Total number of permanent positions	14	14	14
Full-time equivalent of other positions	0	0	0
Average number of all employees	14	14	14
Average GS grade	5.1	5.1	5.1
Average GS salary	$5,822	$6,103	$6,103
Average salary of ungraded positions	$6,777	$6,777	$6,777

Program and financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants:			
(a) Research	67,220	71,631	76,477
(b) Hospital improvement	10,551	10,610	10,610
(c) Training	82,822	92,266	100,762
(d) Fellowships	8,362	9,133	9,859
Total, grants	168,955	183,640	197,708
2. Direct operations:			
(a) Planning, development, and administration of extramural research programs	2,814	2,473	2,550
(b) Intramural research	12,936	13,625	16,114
(c) Manpower and training	1,027	1,653	1,703
(d) Mental health services	934	1,554	1,550
(e) Special mental health programs	1,492	2,287	3,240
(f) Regional and field activities	2,811	4,369	7,588
(g) Fort Worth and Lexington hospitals	8,612	9,246	10,540
(h) Scientific communication and public education	1,268	1,640	2,640
(i) Program management and services	2,627	4,731	4,839
Total, direct operations	34,521	41,578	50,764
Total program costs, funded [1]	203,476	225,218	248,472
Change in selected resources [2]	765		
10 Total obligations	204,241	225,218	248,472
Financing:			
Receipts and reimbursements from:			
11 Administrative budget accounts	−100	−323	−1,727
14 Non-Federal sources (42 U.S.C. 221)	−3	−4	−4
16 Comparative transfers to other accounts	22,450	38,557	
25 Unobligated balance lapsing	6,062	156	
New obligational authority	232,650	263,604	246,741
New obligational authority:			
40 Appropriation	232,669	264,119	246,741
41 Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (79 Stat. 531 and 80 Stat. 674)	−7	−515	
"Office of the Surgeon General, salaries and expenses" (42 U.S.C. 226)	−12		
43 Appropriation (adjusted)	232,650	263,604	246,741
Relation of obligations to expenditures:			
10 Total obligations	204,241	225,218	248,472
70 Receipts and other offsets (items 11–17)	22,347	38,230	−1,731
71 Obligations affecting expenditures	226,588	263,448	246,741
72 Obligated balance, start of year	118,684	176,599	245,108
74 Obligated balance, end of year	−176,599	−245,108	−274,244
77 Adjustments in expired accounts	−4,413		
90 Expenditures	164,260	194,939,	217,605

[1] Includes capital outlay as follows: 1966, $649,000; 1967, $1,163,000; 1968, $1,754,000.

[2] Selected resources as of June 30, are as follows: Unpaid undelivered orders, 1965, $2,659,000 (1966, adjustment, −$38,000); 1966, $3,386,000; 1967, $3,386,000; 1968, $3,386,000.

Community Mental Health Resource Support

Program and Financing

[In thousands of dollars]

	1966 actual	1967 estimate	1968 estimate
Program by activities:			
1. Grants for construction of community mental health centers	39,561	93,092	50,000
2. Grants for staffing of community mental health centers	15,430	32,081	46,168
3. Construction and operation of narcotic addict rehabilitation facilities			4,000
10 Total obligations (object class 41.0)	54,991	125,173	100,168
Financing:			
16 Comparative transfers from other accounts	−15,430	−32,081	
21 Unobligated balance available, start of year	−35,000	−43,092	
23 Unobligated balance transferred to "Hospital construction activities" (78 Stat. 969,970)	1,596		
24 Unobligated balance available, end of year	43,092		
25 Unobligated balance lapsing	751		
40 New obligational authority (appropriation)	50,000	50,000	100,168
Relation of obligations to expenditures:			
10 Total obligations	54,991	125,173	100,168
70 Receipts and other offsets (items 11–17)	−15,430	−32,081	
71 Obligations affecting expenditures	39,561	93,092	100,168
72 Obligated balance, start of year		39,043	129,315
74 Obligated balance, end of year	−39,043	−129,315	−189,483
90 Expenditures	518	2,820	40,000

BIOGRAPHICAL SKETCH OF PRINCIPAL WITNESS

Mr. Flood. We have now the National Institute of Mental Health. The Director is Dr. Stanley F. Yolles. We will place Dr. Yolles' biographical sketch in the record.

Name: Dr. Stanley F. Yolles.

Position: Director, National Institute of Mental Health.

Birthplace and date: New York, New York, April 19, 1919.

Education: 1939, A.B., Brooklyn College; 1940, A.M., Harvard University; 1950, M.D., New York University, Bellevue Medical Center; 1950–51, Intership, U.S. Public Health Service Hospital, Staten Island, New York; 1951–54, Resident in Psychiatry, U.S. Public Health Service Hospital, Lexington, Kentucky; 1957, M.P.H., Johns Hopkins University; 1959, Certified in Psychiatry by American Board of Psychiatry and Neurology.

Experience: Dec. 18, 1964 to present, Director, National Institute of Mental Health;; Oct. 1964–Dec. 18, 1964, Acting Director, National Institute of Mental Health; Aug. 1963–Oct. 1, 1964, Deputy Director, National Institute of Mental Health; Aug. 1960–July 1963, Associate Director for Extramural Programs, NIMH; July 1957–July 1960, Associate Director and Director, Mental Health Study Center, Community Services Branch, NIMH; July 1957–July 1960, Associate Director and Director, Mental Health Study Center, Community Services Branch, NIMH; Jan. 1955–July 1957; Associate Director, Mental Health Study Center, Community Services Branch, NIMH; July 1954–Dec. 1954, Staff Psychiatrist, Mental Health Study Center, Community Services Branch, NIMH; July 1, 1950, Commissioned in Public Health Services; Nov. 1947–Jan. 1948, Guest Lecturer in Tropical Medicine, New York University College of Medicine; Nov. 1945–April 1946, Commanding Officer, Sector Epidemiological Laboratory, British West Indies; Jan. 1943–Nov. 1945, Associate Director, Sector Epidemiological Laboratory; Nov. 1942–Jan. 1943, Parasitologist, Sector Epidemiological Laboratory; July 1941–Nov. 1941, Parasitologist, U.S. Engineer Department, U.S. Army, British Guiana, South America; Oct. 1940–July 1941, Parasitologist, Army Medical School.

Association memberships: American Association for Advancement of Science; American Medical Association; American Psychiatric Association-Fellow; Amer-

ican Psychopathological Association; American Public Health Association-Fellow; American Society of Parasitologists; American Society of Tropical Medicine and Hygience; Group for the Advancement of Psychiatry; Maryland Public Health Association; New York Academy of Sciences; Pan American Medical Association; Washington Psychiatric Society; World Federation for Mental Health.

Other professional Affiliations: August 1962, Chairman Public Health Service Interbureau Committee on Narcotic Drug Addiction; Sept. 1960, Executive Secretary, Mental Health Career Development Program in Psychiatry; 1964, American Medical Association, Mental Health Council, Liaison Officer; 1964, Interdepartmental Committee on Narcotics, Member; 1964, Veterans Administration, Advisory Committee, Psychiatry, Neurology, and Psychology Service, Member; 1965, Member, Board of Editors, Psychiatry Digest; 1965, Associate Clinical Professor of Psychiatry, George Washington University.

Publications: Municipal Government and Community Mental Health, *Public Management*, April 1965; Community Appraisal of Mental Health Practices, *American Journal of Public Health*, December 1964; Local Government Role in Mental Health Programming, *Public Management*, April 1965; The Psychoanalyst and Community Psychiatry, *Science and Psychoanalysis*, Vol. 8, 1965; Community Mental Health: Issues and Policies, *American Journal of Psychiatry*, March 1966; The U.S. Community Mental Health Center Program, *Compherensive Textbook of Psychiatry*, 1966; The Government's Stake in Psychiatric Drug Research, *Psychiatric Drugs*, 1966; The Role of the Psychologist in Community Mental Health Centers: the National Institute of Mental Health View, *American Psychology*, January 1966.

Mr. FLOOD. I notice you have two primary statements here. One is 18 pages and the other is 13 pages. Do you want to summarize them? I have found that with some people it takes longer to summarize them than to have them read. Do you fit in this category?

Dr. YOLLES. If I may, I would like to summarize both of them, one after another, and with your permission present some charts on the overall program.

Mr. FLOOD. Very well.

MENTAL HEALTH RESEARCH AND SERVICES

Dr. YOLLES. Mr. Chairman and members of the committee, the recent establishment of the National Institute of Mental Health as one of five bureaus of the Public Health Service reflects our long-term development of a total approach to the problems of mental health and illness—one that ranges from work in the basic sciences to efforts specifically engineered to advance our skills in prevention and control. This approach emphasizes the overall continuity of the Institute's efforts, for the National Institute of Mental Health, since its inception, has been the principal Federal instrumentality for carrying out a total national mental health program.

Mr. FLOOD. When was it created?

Dr. YOLLES. In 1948, sir.

The programs of the Institute have gradually evolved from a simple beginning program of psychiatric research and mental health training to a highly complex, diversified system of Federal support on a broad national basis which embraces community services, professional and technical assistance, demonstrations, special projects, and training of both professional and nonprofessional workers; in addition to programs of support for construction and staffing of service facilities and the conduct of research.

Mr. FLOOD. You have not worked yourself into a position of being a sacred cow in mental health, have you?

Dr. YOLLES. That position is not always so bad, Mr. Flood.

Mr. FLOOD. Indeed not.

Dr. YOLLES. For many, many years mental health in the United States has been the "low man on the totem pole" so if we are now approaching the sacred cow position it would be a good development.

Mr. FLOOD. What you say is true. It has been a sad history.

Dr. YOLLES. For many years mental health has been so far behind the other specialties in medicine that it became a national disgrace.

PUBLIC ACCEPTANCE OF MENTAL HEALTH PROGRAMS

Mr. FLOOD. There was no public acceptance whatsoever.

Dr. YOLLES. That is right.

Mr. FLOOD. Now you find almost universal acceptance.

Dr. YOLLES. I wish that were so. There is an increasing acceptance.

Mr. FLOOD. I think the acceptance has been extraordinary.

Dr. YOLLES. There has been an extraordinary change in attitude but this is not universal. I think I can summarize this whole approach by one example. You can travel across the United States, for example, by car and become ill with appendicitis any place in the United States and receive rather high-level medical care. No matter what town you are in, it may be Podunk, you will receive a high level of care. But this is not true in the case of mental illness. If you have a mental or emotional breakdown in many places in the United States you will not receive class A care. In many places in the United States even today you will be dumped in a police tank until you can be transported to a mental hospital. For that reason I would like to see it remain a sacred cow until we can get more facilities and more services.

Mr. FLOOD. Even in Podunk?

Dr. YOLLES. Yes, even in Podunk.

Mr. FLOOD. Do you have many problems in Podunk?

Dr. YOLLES. It has been a gratifying experience to see that many of the small towns and rural areas have been able to develop community mental health programs and that they can provide class A treatment for the mentally disturbed.

Mr. FLOOD. You are not inviting patients, are you?

Dr. YOLLES. In a sense, yes, because if you provide facilities, people who have been hidden away and protected are brought out by their families, so you do get an increase in the numbers when you publicize programs of that kind.

Mr. FLOOD. I agree with that. You no longer have them tied to a bed in the attic like animals and it is not wrong.

Dr. YOLLES. At the same time, the Institute's programs have drawn into the mental health field a complex family of diverse disciplines; the biological, the clinical, the service, the social, the cultural, and the behavioral. To carry out its mission of improving the mental health of the people of the United States, it has of necessity been concerned and involved with urban and rural problems, health insurance programs, logistics of mental health care, housing and mental health, human relations, problems of automation, cultural deprivation, as well as a host of others.

LIAISON ACTIVITIES WITH OTHER AGENCIES

On a daily basis, the NIMH works with about 100 units in some 30 other Federal agencies ranging from NASA to Agriculture. Between 80 and 100—about 30 percent—of the Institute's professional staff are engaged in liaison activities with these agencies in a wide variety of fields. In some cases, staff serve full time on detail, or part time with particular agencies, for example, Peace Corps, OEO, HUD, St. Elizabeths Hospital, the National Crime Commission, FDA, and so forth. It is expected that in the course of carrying out its mission, these activities will increase in scope and number.

The resulting heterogeneity of programs and the subtle interrelationship of professional skills bent to a common set of goals has made the activities of the NIMH both the most varied and complex and one of the most delicately interwoven of any set of PHS programs. They offer, however, both the stimulus and the opportunity for innovative approaches and demand new modes of conceptual thought. The resultant research and training activities in the behavioral and social sciences as well as the clinical must range far beyond the traditional biological and biochemical approaches.

PROGRAMS FOR RESEARCH AND UTILIZATION OF RESEARCH FINDINGS

Further, the juxtaposition of service with research programs and of these programs with applied programs has yielded a program pattern within which (a) the findings of research can be most rapidly translated into techniques for treatment and care, and the training of new specialists; (b) developments and findings of control programs at the local and State level immediately signal the need for new emphasis in research, in manpower training, or in the provision of treatment facilities; (c) coordinated mental health data collection activities are simultaneously of immediate use to the bench scientist, to State and local control programs, and to the program planner and policymaker at all levels of government. In short, research, service, control, assistance, training, and demonstration programs have become inextricably interwoven in a basic pattern of mutual reinforcement which can be neither artificially reproduced nor fundamentally modified without program injury.

The mental health program has from its inception deliberately placed special emphasis and has made special programing efforts in the field of application and utilization of research findings.

COMMUNITY MENTAL HEALTH PROGRAM

For example, the Institute has brought together university trainers and State and local users of personnel to plan together. It has involved the universities directly in the new community mental health program and supports over 100 grants in community mental health training alone.

Mr. FLOOD. What is the community mental health training program?

Dr. YOLLES. It is a new approach to dealing with mental health problems in the community in this sense: Over many, many years the kind of treatment given has been on a 1-to-1 basis.

Mr. FLOOD. I have 500,000 people in my district and one psychiatrist and I cannot get any more. I have asked the armed services to beg, borrow, or steal more. Five hundred thousand people and one psychiatrist.

Dr. YOLLES. There is a tremendous shortage of psychiatrists.

A new community mental health center is being developed in one of your counties in Pennsylvania. It will be at Stroudsburg but it will cover Carbon County as well.

In relationship to the community mental health program we are trying to inculcate in the training of psychiatrists a concept of dealing with a community's need and helping to prevent illness, and not solely with the individual who comes in your office and whom you treat four times a week 1 hour a day. This requires a whole reorientation of thinking. In a sense it will overcome in part the shortage of psychiatrists. If you deal with general populations and try to prevent or ameliorate the problems of large groups rather than those of an individual alone, you have far greater success. I do not think any disease has been alleviated or controlled by treatment alone. So it is in the prevention of mental illness in a community that we place our greatest hope.

RESEARCH UTILIZATION CONFERENCE

In research, the "Research Utilization Conference" developed by the Institute has been a most successful tool in translating new findings into practice as well as in training of professionals.

In its report to the President, the Woolridge committee panel on the behavioral sciences concurred in this approach:

> With the accelerated accumulation of new scientific knowledge, it becomes an even more pressing issue to maintain and develop mechanisms for the testing out and translating of fruits of research at the level of practical application. The close link between training and research at NIMH in particular, appears therefore to have been a felicitous development. . . . . What we have said above about the relationship between research and educational functions applies just as well when we consider the relationship between research and community services activities.

The mental health program has grown over the years, but more striking are the dramatic changes which have evolved through use of the total approach in our efforts to improve the mental health of the Nation and to prevent mental illness among its citizens. These changes are the hallmarks of our work, and of our progress. But first let us place the program in perspective. What is the current status of mental health in the United States?

Within the past several years the gravity and urgency ofthe Nation's mental health problem has received substantially increased attention from the general public, from voluntary and professional groups and associations, from the Congress and from the President. The support for an enlarged national effort sprang from a growing awareness of the threat of mental illness to the people of the United States.

THREAT OF MENTAL ILLNESS TO PEOPLE OF THE UNITED STATES

Mr. FLOOD. What threat is there of mental illness to the people in the United States?

Dr. YOLLES. Take one example which we are concerned about. In spite of a declining number of patients in State mental hospitals in the United States, which has been a most gratifying experience, the

number of children under 14 admitted to such hospitals is increasing out of all proportion to either the numbers in the population or in relation to the total patients resident in State mental hospitals.

Mr. FLOOD. Of course the States have been derelict for generations.

Dr. YOLLES. In not providing enough money to staff the facilities properly. The key is in the staffing and not in the size of the institutions because we have seen in the past ten years a change in attitude and a change in approach where you increase the number of people who work with patients. There is a change in attitude, a new hope, as regards chronic mental illness. Backward patients have suffered seriously from what we call an iatrogenic illness, that is an illness created by the doctor. We felt there was no hope and offered less and less. As a result the patients became sicker and became deteriorated. With the advent of the new drugs and new methods these developed new hope and more and more people have been discharged from the mental hospital.

Mr. FLOOD. Have you established halfway houses in this program?

Dr. YOLLES. Yes. These are integral parts of many community health centers which we are supporting now.

There is overwhelming evidence that presently the Nation is neither operating to its capacity in providing adequate programs, services, or facilities for the mentally ill, nor is it utilizing to the fullest extent available knowledge concerning the spectrum of the mental illnesses.

This Nation spends upward of $3½ billion a year on direct mental health services. A very large part of these expenditures is for custodial care and contributes little to the prevention or cure of the mental illnesses. Another $20 billion, it is estimated, is the cost to the Nation indirectly through loss of earnings, loss of output because of excess absenteeism and a lower productivity on the job, loss of tax revenues, etc.

In 1964, it was estimated there were 610,000 psychiatric admissions to general hospitals. If one were to include those admissions which are called otherwise for various reasons, it is likely that the number would reach about two million or about eight percent of all admissions.

About half of the Nation's hospital beds are still occupied by psychiatric patients and it is still true that mental illness touches one family in three and one person in ten requires treatment for a mental disorder at some time during his life. On humanitarian grounds alone our Nation cannot afford the continued loss of human resources represented by 19 million persons with mental and emotional problems.

What progress have we then made?

MENTAL HOSPITAL POPULATIONS

For 11 consecutive years, the resident patient population has decreased in the country's State and county mental hospitals. During the past year, the decline was the sharpest to date—24,000 patients, or 4.9 percent—bringing us at this point to a level six percent below projections made on the basis of earlier downward patterns. Today, resident patients number 452,000—over 106,000 fewer than in 1955 when the downward trend began. If the pre-1955 pattern had continued uninterrupted, there would now be over 702,000 patients in our mental hospitals—a quarter million more than is actually the case. This would have required additional expenditures since 1955 of over $2.5 billion for patient care, and approximately $2.2 billion for the con-

struction of hospital beds. The savings represented here is four times the total NIMH appropriations for mental health programs during the 11-year period.

Mr. FLOOD. Before you go on, you always give us a chart projecting this population.

Dr. YOLLES. Yes. I will submit that later when I get to the charts.

SUICIDE AND THE MAJOR MENTAL HEALTH PROBLEMS

As our program has grown in scope, we have begun to focus our resources on the solution of major and pressing mental health problems. One such problem demanding new and expanded effort is posed by the 20,000 suicides committed annually in the United States. Suicide is the 10th leading cause of death in our country; in the 15 to 19 age group, suicide ranks third, exceeded only by deaths from accidents and cancer; among college students, it ranks second. The toll of suicide, however, cannot be communicated in statistics alone, for its psychological costs are high to both family and community. In addition to the trauma of death itself, each survivor of a suicide—family members, friends, and associates—must handle feelings of shame or guilt. No other kind of death in our society carries such stigma, or creates such lasting emotional scars.

Mr. FLOOD. Do you have anything similar to Alcoholics Anonymous for these people?

Dr. YOLLES. There are a number of them. One is called Rescue, Inc. The Los Angeles center, which is the largest and oldest, has been supported by the NIMH from the beginning.

The Institute's Center for Studies of Suicide Prevention, now under the direction of the Nation's leading authority in the field, will coordinate an attack on the problem, encompasisng support throughout the country of research, training, service, and demonstration activities, as well as of direct research programs within the Institute itself. In the interests of a nationwide prevention program, investigators are developing diagnostic and predictive tests to identify those who are high suicide risks; for example, through measurable changes in certain adrenal hormone levels which may serve as a biochemical indicator of extreme stress, and therefore of suicidal intent in depressed persons.

Our aim is not only to improve therapeutic techniques in dealing with the depressed and suicidal patient, but also to develop a large cadre of professionals in the field—physicians, teachers, lawyers, clergymen, nurses—who are sensitive to new information in the area. Of special importance is the need to recognize the ways in which potential suicides signal their distress, the warnings they inevitably communicate as they desperately seek help. Two-thirds of those who attempt suicide have recently visited a physician, putting physicians, among others, in a strategic position to identify the potential suicide's "cry for help" and to respond adequately.

Through equally intensive and coordinated efforts, we are working toward the solution of other major problems as well; problems posed, for example, by the alcoholic, the drug abuser, the emotionally disturbed child, and the criminal and delinquent in our society.

The span of our efforts in such areas is reflected by our method in approaching problems of crime and violence. At the most basic level,

we are following leads that suggest the possibility of specific drug therapies for offenders, found to be atypical in their responses to medication; in rehabilitation, we are developing programs of education and vocational opportunities for offenders, having demonstrated the value of such programs in reorienting the life of the criminal; and, in the interests of prevention, we are identifying those traits that may be common to offenders, and those characteristics, too, that may be unique to victims of violence. Recently, the Institute began support of a large-scale, university-based center for the study of violence in communities across the Nation. And staff members have served as consultants and advisers to the President's National Crime Commission.

RESEARCH

The basis of all our efforts is the Institute's research program, which continues to grow in size and variety. Over 40 percent of the NIMH research program is devoted to work in the behavioral sciences, encompassing studies designed to identify those physical, psychological, social, and cultural factors that shape human behavior; here too, the NIMH has been at the forefront of change in supporting and enlarging the role and the relevance of the behavioral sciences in the interests of the Nation's health. Such basic studies provide the groundwork for productive clinical and applied research directed toward the resolution of specific problems in mental health.

BIOLOGICAL SCIENCES

In the biological sciences, explorations in basic research have been the springboard for advances in a number of difficult areas, in the containment and control of the schizophrenic's deterioration, in the treatment of depression, in our ability to help decrease the abnormal cravings of the drug addict.

A few decades ago, physical mechanisms in mental illness were seldom the subject of rigorous scientific inquiry. Today, in contrast, studies by increasing numbers of productive scientists are converging on mechanisms in the body—errors in metabolism, or biochemical imbalances—which either trigger or perpetuate pathological behavior in man. Among them are investigators who search for unique blood factors associated with schizophrenia, or the role of brain chemistry in depression, or physical patterns in the addiction to alcohol and to drugs. Already clarified are a number of issues. For example, investigators have shown the causes of phenylketonuria, a form of mental retardation, and techniques for its prevention. And, through work in the Institute's laboratories, scientists are clarifying the mechanisms whereby the body handles catecholamines, those brain and body substances released especially under stress or anxiety, and that play important roles in psychiatric illness and in the patient's response to drugs.

We intend to continue our emphasis on research efforts focused on specific and critical problems. Because, after years of effort, it now appears likely that depression will be among the first major psychiatric illnesses to yield to curative measures, we have begun, for example, to devote increased energies to the development of newer and more rapid acting antidepressants. And, because of the promising new drugs

available to counter drug addiction, we can now develop more effective and comprehensive techniques for treating and rehabilitating abusers. Through such efforts, the Institute will stimulate the continuing interest of the scientific community in the biology of mental illness.

SOCIAL SCIENCES

In the social sciences, too, we are extending and focusing our activities. We are already gaining, for example, a clearer understanding of the importance of early experiences and impressions in the life of the child—how attitudes, values, and standards develop. We are achieving new insights into the complex patterns of family interaction—how they can spawn abnormal behavior and, more important, how the family can be used as an instrument in helping the patient recover; for example, within our own laboratories, investigators have developed techniques to predict the type of psychopathology to be found in an offspring from a knowledge of the style in which family members communicate and relate to one another. We are seeing more clearly some of the psychological and social frustrations that lead to aggressive behavior and delinquency. And, we are tracking the psychological factors that help generate physical illness: recent studies, for example, suggest that feeling of despair and hopelessness in handling a difficult life situation may be associated with the origin of a wide range of physical diseases, even including infectious diseases, cancer, and other disorders not usually associated with psychodynamic factors.

Such work is based on an awareness that man is not only a biological unit, but a social being as well; that he is a product not alone of his body chemistry and neurophysiological makeup, but of his environment, and his culture, and his times. In the field of mental health—more so than in any other field of public health—an understanding of the individual's total life setting assumes crucial importance. Recently, for example, the Institute initiated support of an international pilot study of schizophrenia. Scientists participating in the study, to be pursued by the World Health Organization, will devise and then apply standardized procedures for identifying schizophrenics, for understanding their behavior, and for assessing the effect of cultural and social variables in the disease. Through such studies, behavioral scientists continue their ground breaking efforts to apply the fruits of research to an understanding of the psychological, social, and cultural factors in the etiology, course, and treatment of mental illness.

MULTIDISCIPLINARY RESEARCH

Many of our research efforts bridge the worlds of both the biological and the social scientist. That bridge represents still another important change nurtured and fostered by the Institute: the development of a multidisciplinary pattern in mental health research. The family of scientists in mental health is growing more heterogenious with each passing year, encompassing now a broad spectrum of investigators in the medical, biological, and behavioral sciences.

Typical are those who devote their careers in science to the achievement of a fuller understanding of the complex relationship between man's brain and his behavior—among them psychiatrists, psychologists, biochemists, pharmacologists. A knowledge of the

mechanisms through which the brain and central nervous system control and regulate behavior is essential if we are to fully understand and control emotional disturbances. Investigators are identifying the brain's functions in such human capacities as perception, learning, and motivation. And, they have begun to localize neural centers apparently associated with some basic human drives—including aggressive behavior. Each study provides fresh evidence of the brain's plastic properties, and the potential this gives us for altering aberrant behavior.

Another example of multidisciplinary scientific effort, fostered largely by the Institute, is the growing field of sleep research. In our studies of sleep, scientists have contributed findings of immediate and practical importance—showing, for example, how the identification of a patient's sleep patterns may help us to foresee and treat a variety of emotional disorders. Sleep difficulties are seen today as the precursors of many mental illnesses—the prelude to attacks of depression, and the harbinger of suicide attempts and acute schizophrenic episodes.

RESEARCH APPLICATION

Our progress in research—in understanding some of the enigmas of human behavior—is gratifying. But we are aware that the pace of scientific discovery must be matched by the application of the fruits of the mental health sciences to the pressing and immediate problems of mental health and illness. We continue therefore, to seek opportunities to use basic research knowledge and theory in the solution of the everyday problems of the mentally ill. We have, for example, demonstrated how the intellectual performance of mentally retarded children, suffering the penalties of cultural deprivation, can be improved through the use of carefully programed instruction. We have shown how parole failure rates among delinquents can be reduced; how careful and wise foster placements can transform the destiny of a rootless child; what can be done to restructure the tangled life of the unwed mother; how the aged can be helped to a life of greater service and serenity; and how the chronically ill mental patient can be motivated to function more independently and productively. Such efforts have had a remarkable and cumulative effect: they have worked a revolution of change in society's attitudes toward the mentally ill—bridging the psychological gap between the isolated hospital and the community; and they have restored dignity and hope to the millions among us who are victims of mental illness.

IMPROVING STATE HOSPITAL PROGRAMS

We are transforming, too, the character of the State institution and its role in the care and the treatment of the mentally ill. For over a century, America's State mental hospitals have been the major resource available for the seriously disturbed, virtually their last hope for psychological survival. Although our community mental health programs are fast changing the face of mental health care across the country, we must nevertheless continue to devote our urgent concerns to those patients who must still be cared for and treated in existing mental hospitals. This we have done—to the lasting benefit of thousands of our mentally ill.

In the years since the inception of our hospital improvement grant program, awards have been made to over half of our State institutions for the mentally ill and retarded. Every State has received at least one grant, and 18 have grants for all of their eligible institutions. Improvements in therapeutic services have now reached nearly 200,000 hospital patients—the emotionally disturbed child and the senile psychotic, the mute depressive and the agitated criminal offender, the acute schizophrenic and, perhaps most important, the chronic patient who has languished in the back ward, a prisoner of outmoded medical care. In a related program, over 50,000 hospital attendants and aids have improved their skills, as nearly two-thirds of all eligible State institutions have participated in our inservice training program. We have thus enhanced the capacities of those who remain a major source of human contact for the mentally ill.

MANPOWER

All of the goals we seek continue to demand the most skilled manpower our country can supply. And here, too, our efforts have wrought change. The scope of the Institute's training programs extends today beyond those disciplines traditionally recognized as the "core" of mental health manpower—psychiatrists, psychologists, social workers, nurses. We have increased that core by nearly half since 1960—from 44,000 to 64,000. But equally important, our efforts now reach a new range of individuals to whom those in trouble often first turn for help—clergymen, judges, teachers, administrators—all of whom have now begun to work toward the improvement of preventive mental health services, and the treatment of the mentally ill. Through pilot and experimental projects, we continue also to create innovating training programs, many of them emphasizing new concepts of community-based mental health services.

INFORMATION ACTIVITIES

In support of all its efforts, NIMH continues to pursue vigorous information programs directed both to the professional and lay public.

I would like to turn over to the committee a new report, just off the press, by the Institute on some of the newer research findings.

These activities aid in the interchange of current data among scientists, in the communication of the latest findings to those in the best position to apply to new knowledge, and in the dissemination of useful mental health information to the public at large.

The National Clearinghouse for Mental Health Information provides a growing base for the collection and utilization of current knowledge in the mental health field. The Clearinghouse functions as a center for the evaluation of scientific information—collection, processing, and disseminating data in such varied fields as drugs abuse, psychopharmacology, occupational mental health, and schizophrenia. With the growth of its technical capacities, the services of the Clearinghouse now reach increasingly large portions of the research and clinical communities—for example, through a growing output of published reports. Currently, too, over 50 requests per day for scientific information on specific subjects are received and answered as part of the developing array of activities of the Clearinghouse.

The public information activities of NIMH are also growing to meet the mental health needs of our citizens. To advance the community mental health centers program, for example, that program has been the subject of a series of special publications, magazine articles, newspaper stores and features, exhibits, TV programs, and motion pictures. And, as one more example, information on drug abuse has been disseminated in the form of nearly 2 million copies of a special booklet directed at young people. Through such activities, the Institute continues to insure that the gains made through technical and scientific endeavors will be put to use by an informed citizenry.

A NATIONAL PROGRAM

In our total efforts, we have not acted alone; we have been partners with American society. Our role has been not only to induce change, but to respond to the changing needs of our society—to the stirring of new and growing mental health problems on the American scene. In fact, the new organizational structure of NIMH reflects that dual process. We will continue, for example, to develop new vistas in clinical and behavioral research; but we have also reacted to the need for focused studies—stimulated, for example, by our burgeoning problems of metropolitan life. We will continue to prod and stimulate changes in outmoded traditions of mental health care; but we have also organized special centers to cope with the need for new knowledge and new techniques to deal with mounting public health problems such as suicide, alcoholism, drug abuse, and crime and delinquency. Our advances vindicate our approach. Ours has been change idly pursued for the sake of change alone; rather, our altered concepts and techniques are rooted in scientific inquiry and careful assessments of alternatives.

In building our programs, we seek the considered advice of national leaders in all areas related to mental health. Toward this end, the Institute recently invited over 200 persons—from academic and research settings, State programs, voluntary and citizen organizations, and legal agencies—to serve as members of ad hoc advisory committees in areas ranging from schizophrenia to metropolitan mental health problems, from behavioral science to mental health financing.

Through such activities, we propose to maintain rapport with professional and lay leaders across the Nation. Because we are concerned with man's total behavior, we are attuned to the major tides and pressures of American life. Our overall mission has not changed. It remains simply to improve the mental health of the people of the United States. Toward this end, we shall integrate our efforts in the mental health field with our Nation's quest for better health for all of our citizens.

BUDGET REQUEST

The request for 1968 is $248,472,000 as compared with an operating level in 1967 of $227,218,000. There is an increase of $21,254,000 which is spread among the activities of the Institute for on-going and new programs. Shall I proceed to summarize the other statement?

Mr. FLOOD. I think so.

COMMUNITY MENTAL HEALTH RESOURCE SUPPORT

Dr. YOLLES. Mr. Chairman and members of the committee, 21 years ago, when the National Mental Health Act was passed, only very few workers in the field were concerned with the development of community mental health services. Even to them, the goal of effective services near home seemed distant and remote, barely visible on the horizon. The limited community mental health facilities of the day served primarily as transfer agents—between the shattered lives and homes of citizens and the back wards of custodial institutions. Across the country, the American's attitude toward mental illness was still heavy with centuries-old traditions of shame and fear.

The challenge was great and it could not be denied—a challenge embodied in those hundreds of thousands of mentally ill Americans, whose doom was being inexorably sealed in isolated hospitals across the country. Today, only three years after the passage of the historic Community Mental Health Centers Act, we can gauge the degree of our progress: Our Government has now supported the development of 172 community mental health centers, with funds totaling $73 million to be devoted to the dual tasks of construction and staffing. These centers—the symbols of a new era in mental health care—serve 44 States and territories. They have sprung from the creative collaboration of mental health professionals, and political and civic leaders at the Federal, State, and local level. And, they have evolved from a solid base: a broad range of public and private agencies—hospitals, clinics, medical schools—many of them combining their efforts to develop a single comprehensive center.

Mr. FLOOD. Channeled through the respective State agencies, or directly to the local agencies?

Dr. YOLLES. In construction, the program is based on a formula grant program, and therefore goes through the State. The staffing program is a project grant program which we have modified so it is a quasi-formula grant program. We have made allocations to each one of the States, and we have asked the State agency concerned for its opinion of each project as it comes in.

MEASURES OF PROGRESS

It is important at this point to assess the shape as well as the degree of our efforts. We must evaluate the extent to which we are meeting the criteria of quality we set for ourselves and for the millions of citizens who are the potential beneficiaries of this contemporary approach.

The program requires, for example, that each community mental health center make its services not only available, but readily accessible to all. How have the results of our efforts matched this objective?

It was clear from the outset that communities seeking support for mental health programs would ultimately represent a sweeping cross section of the total American community. Initiative has come from depressed areas and from regions of great wealth; from one-industry towns to cities built on a broad industrial base; from areas containing some of the strongest medical centers in the country to those which have until now attracted few or no professionals in the mental health field.

Mr. FLOOD. Have you discovered one single problem cutting across them all?

Dr. YOLLES. No, two of them have been quite the same. The closest we come to a problem which is universal is the one of manpower. Even in this, we have received some surprises. We had thought that rural areas would have some difficulty acquiring and retaining personnel. It has been interesting to observe that they have done very well.

For example, in North Dakota they expect to obtain personnel they need for the proposed five centers which they have underway.

Mr. FLOOD. What did they do? Trap them?

Dr. YOLLES. One of the elements in this is that the staffing legislation enables the State to be more liberal in terms of employment than many State agencies have been able to be in the past. For example, it allows educational leave for persons supported and a number of other "fringe" type benefits.

Mr. FLOOD. Does this not result in piracy within the State institutions?

Dr. YOLLES. So far there has been relatively little piracy. Let me put it another way: So far there has been no more than usually goes on between State institutions. We have been very heartened by the ability of some of these areas to acquire personnel. As I mentioned before, in the North Dakota situation, when all centers are funded which we expect within the next year or so, North Dakota will have for 90-plus percent, a current mental health center within an hour's drive. This is a remarkable achievement.

SIZE OF POPULATION CONCENTRATIONS SERVED BY MENTAL HEALTH CENTERS

The image of the mental health center as serving populations concentrated only in the metropolis is hardly valid. The developing centers are marked by a broad regional diversity; a third are in cities of a half-million persons or more; another third in cities of 50,000 to 500,000; and a final third in communities of 50,000 residents or fewer. Mental health services will thus reach big-city dwellers, suburbanites, and rural residents alike. In fact, nearly 150 predominantly rural counties are included in the population areas served by centers now being formed; residents of many areas will now have mental health professionals in their midst for the first time.

RANGE OF SERVICES PROVIDED BY MENTAL HEALTH CENTERS

What about the range of services provided?

On this score, too, the program requirements were clear. Each center, they prescribed must assure continuity of care—encompassing five basic treatment services: inpatient services for those who may require short-term hospitalization; partial hospitalization—during the day or overnight; outpatient treatment for patients who might make appointments as they would routinely with their family physicians; emergency services, available around the clock; and consultation and education programs to other agencies dealing with persons who are mentally and emotionally disturbed.

How have we fared?

The center programs, I am pleased to report, are evolving as they were intended to—with a spectrum of services by mental health workers who seek to equal the range of needs brought by citizens in search of help. A number of the centers now underway sprang from agencies already providing nearly the entire span of essential services. But the program has also given sharp rise to many new and improved services in communities across the country:

New inpatient services will be available in 40 percent of the centers funded, and in an additional 32 percent they will be enlarged—either through new physical facilities, increased staff, or both.

Over half of the centers currently underway will provide partial hospitalization facilities in areas where no such capacity existed before.

New outpatient services will be offered by 45 percent of the current centers, and an additional 40-percent plan to improve and expand existing therapeutic approaches used on an outpatient basis—including individual and group psychotherapy, family therapy, and drug treatment.

Half of the centers will offer new emergency services, and a third more will increase them beyond their present levels; many plan to publicize emergency facilities widely within the community in order to assure their increased use.

STAFFING FOR MENTAL HEALTH CENTERS

Mr. FLOOD. What would the staffing pattern be?

Dr. YOLLES. It varies. A new center starting from scratch, for example——

Mr. FLOOD. In a medium-sized city.

Dr. YOLLES. It is a little difficult to describe without knowing what facilities are presently available. As I was going to say, if you started from scratch in an ideal situation, where you have all the personnel you need and all the support, we estimate needing about 100 or 110 persons for a community mental health center, professional and subprofessional personnel, to take care of all the five essential services.

In some areas, part-time personnel would be used, and in many areas they are being used.

Mr. FLOOD. You mean utilizing existing facilities or building new facilities?

Dr. YOLLES. The 108 persons were for a total new service, whether already constructed or put together de novo within an existing building. The average staffing pattern of all community mental health centers funded so far shows about 50 persons. A large percentage of them are part time; so you have many more persons actually employed. All of them have psychiatrists, psychologists, social workers, and nurses. Then there is a variety of other individuals, depending upon how comprehensive the center may be.

Mr. FLOOD. Did you and I ever agree upon what is a psychiatrist and what is a psychologist?

Dr. YOLLES. I am not sure that you agreed with me, Mr. Chairman, but I think I defined it for you last time I was before you.

Mr. FLOOD. Suppose you do it again.

Dr. YOLLES. A psychiatrist is a physician who is trained in the diagnosis, care, and treatment of mentally and emotionally disturbed indi-

viduals. A clinical psychologist is a scientist with a Ph. D. degree usually, who has received extensive training in the diagnosis as well as the care of persons who are mentally and emotionally disturbed. In the case of the clinical psychologist and the psychiatrist, there is a great deal of overlapping, especially in the diagnosis of cases, less overlapping in the treatment area. There are many types of psychologists. There are experimental psychologists who concern themselves with laboratory experiments in the field of behavior, for example; there are social psychologists, and so forth.

Have I clarified it for you?

Mr. FLOOD. Yes, I think so.

Dr. YOLLES. Forty percent of today's centers will offer new consultative services, and another 40 percent will broaden existing ones—reaching out to schools, churches, court and juvenile authorities, and welfare agencies.

The community mental health centers program was a bold confrontation of the almost universal problem of fragmentation of services—in which the interests of professional agencies reigned supreme over the needs of the patient and his family. The program placed the patient at its hub, and citizens and professionals alike responded. Already, the community mental health center has served as a model for other programs—from neighborhood centers to community delinquency programs—in which comprehensive and continuous services must replace fragmented and overlapping ones.

MEETING SPECIAL NEEDS

These data do not imply a rigid uniformity among the centers. Far from it. There is no single profile, for no two American communities are alike. Each center has its individual characteristics—reflecting the needs and the resources of the area it serves. The range portrays the face of America, and the ingenuity and adaptive ability of its citizens. Some centers, for example, will reach out to crowded metropolitan areas, while others will spread their services across thinly populated mountains and plains. In Texas, Dallas will have a full span of mental health services based in the city's large general hospital. In Louisiana, in contrast, two agencies have devised a plan to serve the people of the bayou country through individual clinical units ranging over four counties; and in Kansas, two agencies have combined to provide comprehensive services to residents of a rural area spanning over 20 counties.

PATTERNS OF FINANCING

The diversity of the center programs is further reflected in funding patterns used across the country. In some States, Federal money is being matched with State money exclusively; in others with State and local money; in still others with private funds. We are encouraging the broadest possible base for the financing of community mental health centers, and some communities have pioneered new funding programs among several counties or regions, and across State lines.

As a result of the community mental health centers program, many States have sought to involve their communities directly in the provision of mental health services. The most common mechanism has

been a State-implemented Community Mental Health Services Act. Since the passage of the first such act in New York 13 years ago, 28 States have followed suit. These laws have provided for decentralization in the administration of community services, cost sharing by the State and localities, and the maintenance of local choice and initiative; State funds have typically been provided on a matching basis.

Within the last year, several States have considered and passed community mental health services legislation. Perhaps the boldest approach to date has been the recently developed Services Act in Pennsylvania. The Pennsylvania act insures that the localities of the Commonwealth provide a wide range of mental health services, and pledges State support of 90 percent of eligible costs.

It is a source of satisfaction for us to note that community mental health center financing efforts have often grown from the deepest roots of the community—from the citizenry itself. The Lane County Community Mental Health Center in Eugene, Oreg., for example, is largely the result of community sponsorship; seventeen county agencies are affiliated with the center, which will serve residents in an area reaching from the Pacific Ocean to the summit of the Cascade Mountains, as well as the 12,000 students at the University of Oregon in Eugene. In Pittsburgh, a grant from the Appalachian Regional Commission will help in the realization of a center to serve an area of 160,000 residents—primarily from low-income, urban areas. At Daytona Beach, Fla., the Volusia County Mental Health Center is the result of a unique community drive to guarantee adequate mental health services. The local mental health association initiated a campaign to raise money toward construction of the center, and the largest corporation in the county contributed the services of its public relations department to promote the drive. Civic groups and hundreds of individuals participated—physicians, bankers, lawyers, housewives; one resident contributed the income from an orange grove to the project; the clergy sponsored a mental health Sabbath. Most important, the total effort brought all the interests within the country together for the first time in its history.

RELATED PROGRAMS

Such episodes are dramatic and revolutionary—all of them part of the era of change that has begun in mental health care. But the community mental health center program, despite its newness in concept and design, does not exist—cannot exist—apart from other programs and other advances in the mental health field.

The success of the centers effort must rest heavily, for example, on our basic and applied research programs; programs designed to develop and refine the kinds of techniques that will serve our citizens along the entire continuum of help they may need: milieu therapy for the aged inpatient; family therapy for the adolescent outpatient and his parents; aftercare for the successful adjustment of the recovered patient in his home and community; or, crisis intervention procedures to prevent serious and chronic disruptions of the patient's life. Still another instance arises from the field of psychopharmacology, in which our development of drug therapies has been basic in the movement toward community mental health care. In a decade, the use of drugs has helped shift the focal point of treatment from the hospital to the

community, until today, the mentally ill being treated at home probably outnumber our 450,000 hospital patients by a ratio of 5 to 1.

It is not only our research programs that affect the destiny of the community mental health center program. Even more crucial to the success of the overall effort, for example, are our training programs through which we are enlarging the pool of manpower which must ultimately meet the realities of community treatment and, in the final analysis, actually deliver the services. And, as one more example, our field and technical assistance activities are helping to develop the kinds of consultative services in the States which represent one of the most important innovations of the centers program. For it we are to reduce significantly the toll of mental illness, it will be through preventive programs—and these hinge on the quality of the consultation provided to schools, to courts, or to welfare agencies.

SPECIAL SERVICES FOR CHILDREN

The centers have also met the special needs of those addicted to either drugs or alcoholics, and for children.

Mr. FLOOD. Do you mix children with adults?

Dr. YOLLES. Yes, sir. The pattern in the United States for many years in community mental health clinics has been to treat both children and adults. Within the past 12 to 15 years, there has been a growing development of specialized services for children. As yet, the number of child psychiatrists in the United States is relatively small. In State hospitals or residential institutions, we would prefer children not to be in residence with adults, but in out-patient clinics it makes relatively little difference, because they can be treated at different times. The techniques and the approach are different.

DRUG ABUSE PROGRAM

I would like to speak briefly about our program in drug abuse, which is growing in size and scope.

With the reorganization of the Public Health Service, the Fort Worth and Lexington hospitals have been transferred to the National Institute of Mental Health. The role of these hospitals will be modified in time from one designed primarily to provide care to addicts, to one aimed at developing new knowledge and new methods of intervention, treatment, rehabilitation, and aftercare in the fields of drug abuse, drug dependence, and specific personality disorders. In keeping with these goals, the two institutions have been redesignated as Clinical Research Centers—thus filling a gap in the Nation's present clinical research resources directed toward problems of drug abuse.

The conversion of the hospitals' roles will be delayed to some degree in the interests of implementing the Narcotic Addict Rehabilitation Act of 1966. This act has authorized the commitment for treatment and rehabilitation of narcotic addicts who come before Federal courts in any of three different ways: Those charged with a nonviolent crime against the United States and committed to treatment in lieu of trial; those tried and convicted of a crime against the United States and sentenced to commitment for treatment; and those not charged with any crime who are civilly committed for treatment. Much of the responsibility for carrying out the provisions of this act is now vested in the

Public Health Service—with the balance of responsibility carried by the Department of Justice. Accordingly, in the early years of implementation of this legislation it will be necessary to continue to use the Fort Worth and Lexington facilities for the examination of alleged addicts and their institutional care.

Besides changing the legal criteria for eligibility for treatment at the Federal level, the legislation also authorized activities which the Public Health Service could not carry out before. The most important of these is the authority for the Surgeon General to provide supervised aftercare services (for those addicts in his custody) averaging 2½ years following their release from inpatient treatment. It has been lack of aftercare facilities, many professionals in this area believe, which has resulted in the high rate of recidivism among addicts released from institutional care.

In keeping with community mental health concepts and to insure that close followup and supervision of the addicts will be maintained aftercare will be carried out on contract by appropriate facilities near the homes of the addicts. To maintain an overview of the performance of the contracts and insure a high level of professional performance in aftercare and rehabilitation, it is planned to locate Public Health Service personnel in the 11 metropolitan areas having the largest addict populations.

GOALS AND PROSPECTS

The outlook, then, is a positive and promising one—reflecting substantial progress in the community mental health center program itself, and in the allied programs of the Institute converging on that effort. This statement would be incomplete, however without an acknowledgment of the problems we must yet face.

We must continue our efforts to fill the enormous reservoir of manpower demanded by the center's program, without which our highest purposes will be frustrated.

Through careful research, we must continue to pursue the kinds of creative approaches to the treatment of the mentally ill that alone can give true meaning to the estabilshment of comprehensive services.

We must encourage close collaboration among the many professional disciplines working in the interests of the Nation's health, molding them into the kinds of compassionate staff that best serve the patient's interests.

We must assure that existing patterns in the financing of mental health services are maintained and strengthened in the States and communities across the Nation.

Despite our progress, we must be constantly aware that the Nation's need is still great—that nearly half a million Americans continue to reside in mental hospitals, and that a third of our citizens are significantly impaired at some time in their lives by symptoms of mental illness. We have made only a modest start in meeting the mental health needs of the American people; the great bulk of our population remains to be served through the 2,000 centers planned by 1980.

Difficult tasks and obstacles are still clearly before us, yet I have no reason to doubt that we will succeed. This conviction arises out of the confidence and strength we feel as partners with communities throughout the Nation. Ours is a cooperative venture embracing var-

ious segments of society. Across the country we have stimulated a wave of rising hopes. We shall continue in our efforts to satisfy those hopes and thereby advance the well-being and productivity of our people.

COMMUNITY MENTAL HEALTH RESOURCE SUPPORT

The request for 1968 is $100,168,000 as compared with an operating level in 1967 of $125,173,000. There is a net decrease of $25,005,000. This decrease is discussed in detail in the budget justification. The request for 1968 is distributed as follows: Grants for construction of community mental health centers, $50 million; grants for staffing of community mental health centers, $46,168,000; construction and operation of narcotic addict rehabilitation facilities, $4,000,000. The total 1968 appropriation request is $100,168,000.

I would now like to present these charts.

SUMMARY OF RESEARCH PROJECTS

The NIMH program consists of a family of programs. Intramural research, where we do our own research at Bethesda and our field stations. Extramural research support, research grant support, training grant support, the construction of community mental health centers, the staffing of community mental health centers, scientific communication and public information, direct training of our own personnel, biometry programs to report on the extent of mental illness in the United States, grants-in-aid to the States for development of programs in the communities, and professional and technical assistance by NIMH personnel to States and communities.

Mr. FLOOD. How close do you bird dog the State grants on these things?

Dr. YOLLES. In terms of formula grants to the States for grants-in-aid, we maintain quite close liaison. In research grants, it is far less. In terms of the hospital improvement grants we make to State institutions, we have considerable followup.

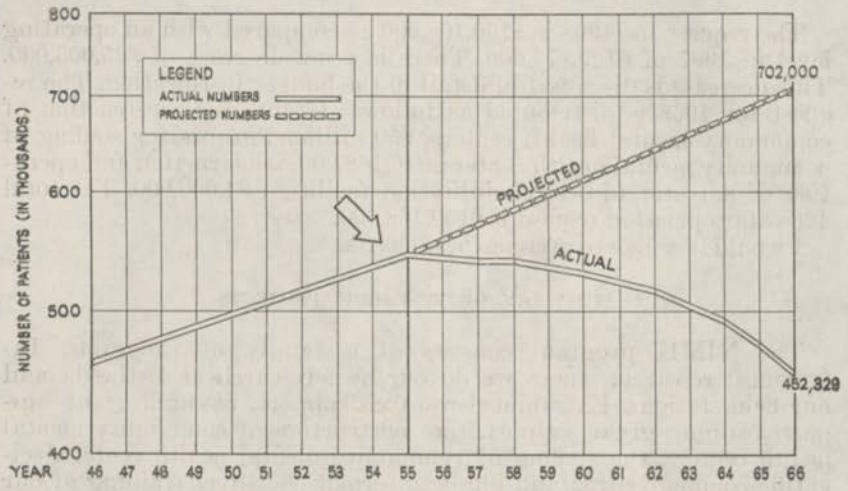
Mr. FLOOD. I would be worried about the latter.

Dr. YOLLES. The State institutions or the followup?

Mr. FLOOD. State institutions.

Dr. YOLLES. We have been anxious to improve the level of care in these institutions as an interim program until the community mental health centers are ready to take over the burden of care. So, we have sent our personnel in to see that these programs are improving.

TREND IN NUMBER OF RESIDENTS IN STATE MENTAL HOSPITALS

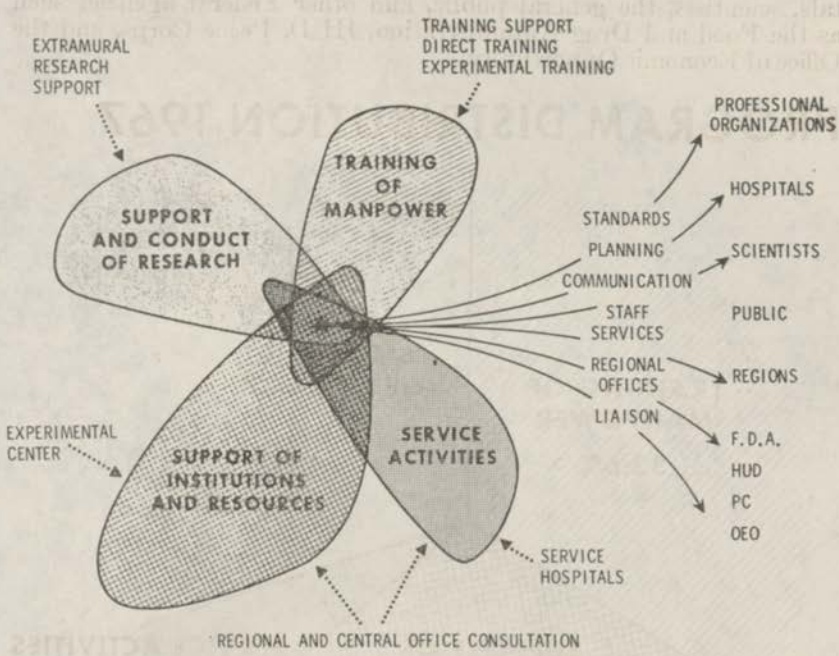


This is a reflection of the changes that I mentioned before. This is the trend and the actual numbers of patients resident in State mental hospitals over the years starting in 1946 through 1955, with a steadily increasing upward rate, with increasing numbers resident in State hospitals at the end of each year.

In 1955, we have the first break in this upward trend. The introduction of the psychoactive drugs, the tranquilizers, plus the development of community facilities, the introduction or the expansion of the treatment of the mentally ill and emotionally disturbed in general hospitals, plus this new wave of hope that I was talking about before, have been reflected in this decreasing number of patients in the State mental hospitals.

If this trend had continued unabated, we would have about 702,000 patients in mental hositals today. Actually, we have as the year total for 1966 an average of 452,000 patients. This difference in number has resulted in the cumulative saving of $4.7 billion which was used by the States and communities otherwise than for the care of patients

FOUR MAJOR PROGRAM AREAS



These are the four major program areas of the Institute: The support and conduct of research, training of manpower, service activities, and the support of institutions and resources.

The value of the total program is that all of these program areas feed back into one another so that one becomes modified by the results of the other. The training of manpower is affected by the results of research. New findings from research can immediately be translated and incorporated into the training of new manpower. Likewise, the findings in training can be incorporated into the support of institutions and resources in the field.

Often in our service activities, new pragmatic findings in the field are fed back into the support and conduct of research for further refinement. A clear example of this is the treatment of families as a unit rather than a single individual.

We start it in practice first, and then feed it back into research to be refined as a treatment technique.

Mr. FLOOD. How does the AMA consider you? Respectable?

Dr. YOLLES. Yes, sir. The American Medical Association recognizes mental health as the No. 1 health problem in the United States.

Mr. FLOOD. I know that, but I mean your operation.

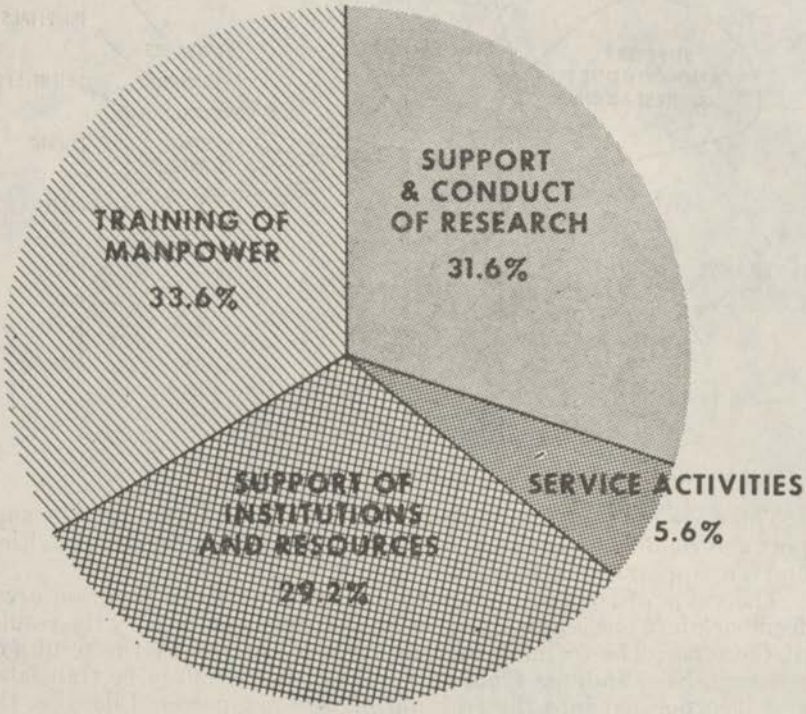
Dr. YOLLES. Eminently respectable, Mr. Chairman.

All of these findings and their modifications by relations to other elements of the program are fed out from the Institute by means of our staff services, the setting of standards, not the enforcement of standards but aiding professional organizations in setting standards for care, planning, communications, and staff services of other types.

Through our regional offices, and the liaison with other agencies,

these findings are disseminated to professional organizations, hospitals, scientists, the general public, and other Federal agencies such as the Food and Drug Administration, HUD, Peace Corps, and the Office of Economic Opportunity.

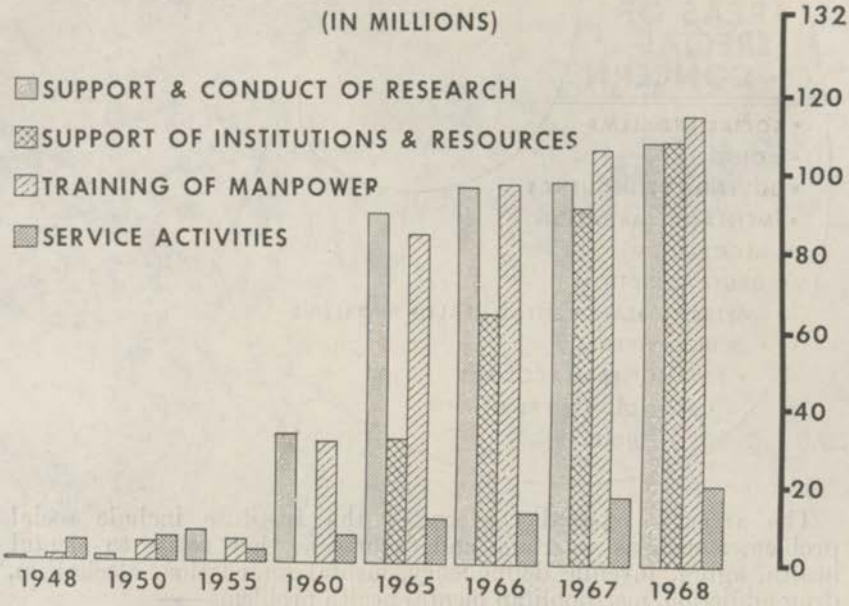
PROGRAM DISTRIBUTION 1967



This is the general distribution of the program in 1967 to show the rather equal distribution of the three parts of the program. We have been concerned that we have a balanced program between the training of manpower, the support and conduct of research, and the support of institutions and resources.

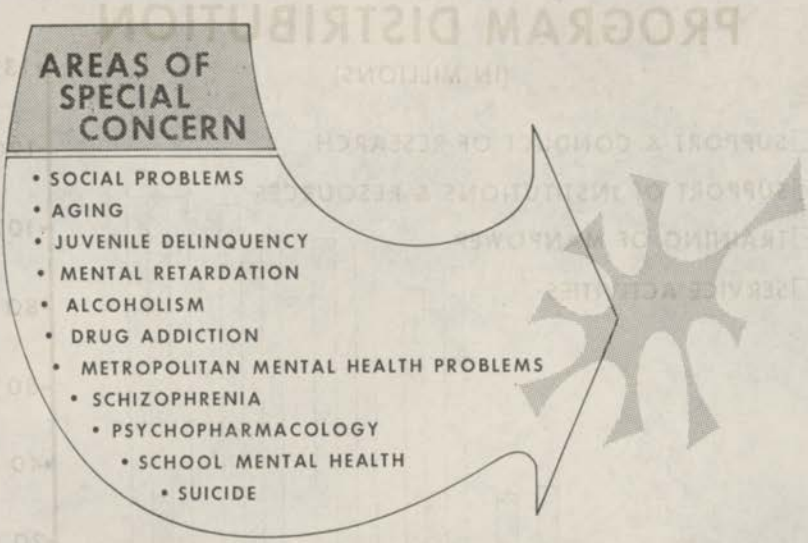
PROGRAM DISTRIBUTION

(IN MILLIONS)



This reflects the program distribution over the years.

As you note, when we started in 1948, the support of institutions and resources was not available to us. With the passage of the Community Mental Health Centers Act and its implementation in 1965, you notice the red column comes in, and we now have more or less equal distribution of program elements.



The areas of special concern of the Institute include social problems; such as marriage and divorce as they relate to mental health, aging, juvenile delinquency, mental retardation, alcoholism, drug addiction, metropolitan mental health problems——

Mr. FLOOD. Is there any significance in the way you have them listed?

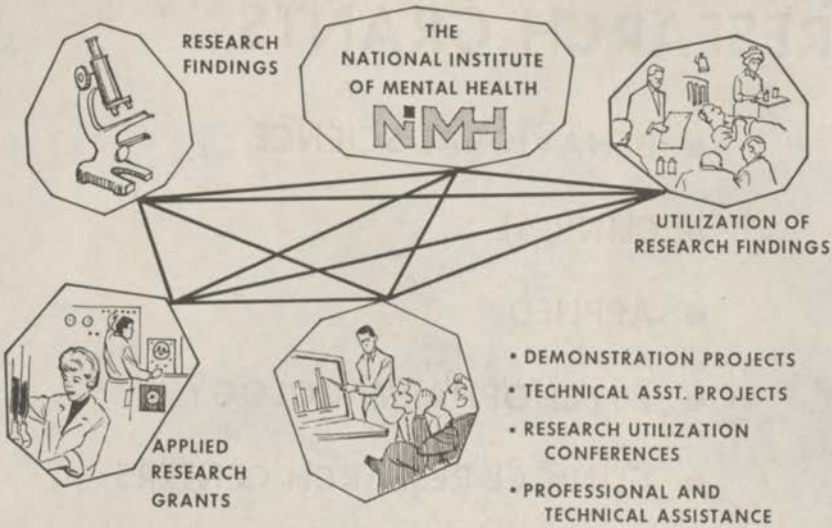
Dr. YOLLES. No, sir; schizophrenia, psychopharmacology, school mental health, and suicide.

TYPES OF RESEARCH GRANTS

- BEHAVIORAL SCIENCE
- CLINICAL
- APPLIED
- PSYCHOPHARMACOLOGY
- CLINICAL RESEARCH CENTERS
- HOSPITAL IMPROVEMENT PROJECTS
- GENERAL RESEARCH SUPPORT

This is merely a listing of types of research grants we have, ranging from behavioral sciences to clinical research grants, applied research grants, grants in the area of psychopharmacology, clinical research center support, hospital improvement projects, and general research support grants to universities.

UTILIZATION OF RESEARCH FINDINGS

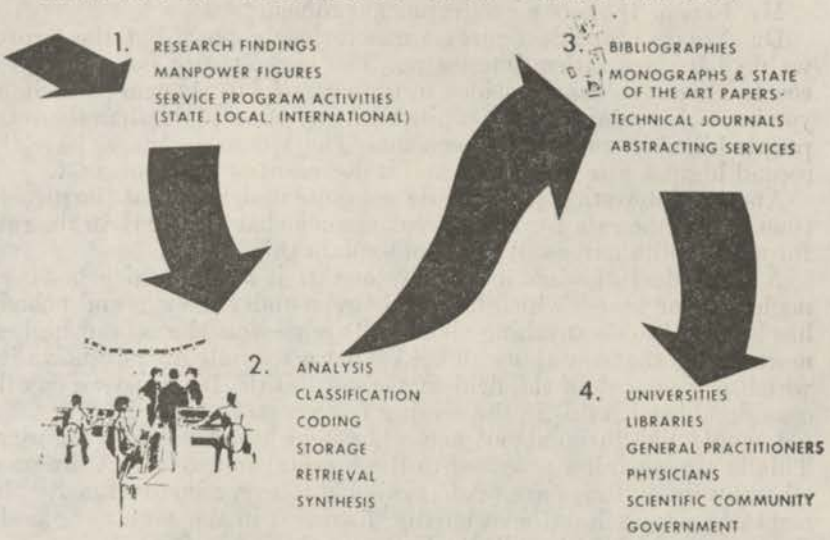


Perhaps our most interesting approach is through the utilization of research findings. Findings in the laboratory and the field are fed back to the Institute. The Institute supports attempts to utilize the research through applied research grants, and through demonstration projects. Attempts are made to utilize the findings.

Final application and utilization are through the means of demonstration projects, technical assistance projects which we support in the States, research utilization conferences, and professional and technical assistance by our own staff. The latest findings are thus available to States and communities.

Again to aid in the application of our findings, the dissemination of information is through the National Clearinghouse for Mental Health Information. Research findings, manpower figures, service program activities, State, local and international, are fed into the clearinghouse where they are analyzed, classified, coded, stored, retrieved, and synthesized and fed out in the form of bibliographies, monographs and state-of-the-art papers, technical journals and abstracting services. These are available on request to universities, physicians, libraries, the scientific community and Government.

THE NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION



In the area of training, this represents the distribution of our training funds by specialized area. In the field of psychiatry, you notice about $28 million in grants during 1967. Behavioral sciences, $18 million. Psychiatric nursing, $10 million. Social work, $12 million. Narcotics and drug abuse, alcoholism, metropolitan mental health problems, suicide prevention, the general practitioners' program, a very successful program for training general practitioners not only as psychiatrists, but also in another part of the program to give short courses in psychiatry to general practitioners.

Mr. FLOOD. Suicide prevention? How do you prevent suicide?

Dr. YOLLES. One of the interesting phenomena in suicide is that about 86 percent of all successful suicides have given notification to a physician or to some other key person of their intent to do so. This is most often in hidden fashion. The recognition by professionals of that "cry for help," as we call it, is the first step in suicide prevention.

We would expect that if we train enough key professionals—physicians, ministers, and lawyers, who are the key groups—to recognize this communication, we can perhaps reduce the number of suicides in the United States by about 25 to 30 percent.

Secondly, we deal with recognition, in terms of research findings. There are distortions of sleep patterns, distortions of endocrine levels, et cetera, all of which may be harbingers of suicide.

Then there are other certain signs which may be available. The teaching of all of this, I think, will result in a grossly reduced rate of suicides in the United States.

Mr. FLOOD. Is there a geographical problem?

Dr. YOLLES. Suicide figures are notoriously poor, but the figures we do have are rather interesting. The highest rate is on the west coast. There are more suicides in the city of Los Angeles, which, as you know, has more cars per capita than any other place, than there are people killed in automobile accidents. The Mountain States have the second highest rate of suicide, and it decreases as you come east.

Another interesting point we do not quite understand at the present time is that the rate for rural areas is somewhat higher than the rate for metropolitan areas. We cannot explain this.

A great deal of work has to be done. It is a field which has been neglected for years; which has been swept under the rug and nobody has bothered to do anything about it. It represents the aera of highest mortality in the mental health field. That is the only area of mortality which is clear cut in the field of mental health. We hope we can do considerable with this in the coming few years.

I would like to point out one other item here: inservice training. This is a companion program to the hospital improvement program whereby grant funds are made available to every institution for the mentally retarded and emotionally disturbed in the country to train the personnel in the hospital, to improve the level of care.

TRAINING FUNDS BY MENTAL HEALTH SPECIALTY 1967

PSYCHIATRY	$27,880,000
BEHAVIORAL SCIENCES	$18,000,000
PSYCHIATRIC NURSING	$10,300,000
SOCIAL WORK	$12,300,000
NARCOTICS AND DRUG ABUSE	$137,000
ALCOHOLISM	$256,000
METROPOLITAN M.H. PROBLEMS	$25,000
SUICIDE PREVENTION	$250,000
GENERAL PRACTITIONER	$9,850,000
EXPERIMENTAL AND SPECIAL	$5,800,000
CONTINUING EDUCATION	$2,800,000
INSERVICE TRAINING	$4,668,000
TOTAL	$92,266,000

In terms of meeting our needs by 1980 for the 2,000 or so community mental health centers projected for that time, we have developed our manpower needs back in 1962. The blue line shows the development of

nursing personnel. The orange line, the second one down, shows the number of psychiatrists. Psychologists in green, and social workers in black.

An interesting phenomenon is that between 1960 and 1965 there has been a growth in the mental health professions of 44 percent as contrasted with an 18-percent increase in the major health professions of medicine, dentistry, environmental health, nursing, and health research.

Mr. FLOOD. Why?

Dr. YOLLES. This was a deliberate approach on the part of the administration to increase the number of mental health professional personnel. At the time the Community Mental Health Centers Act was being considered, at the time of the implementation of the report of the Joint Commission on Mental Illness and Health, it was argued that there would not be enough personnel to go around. This was a major point of concern.

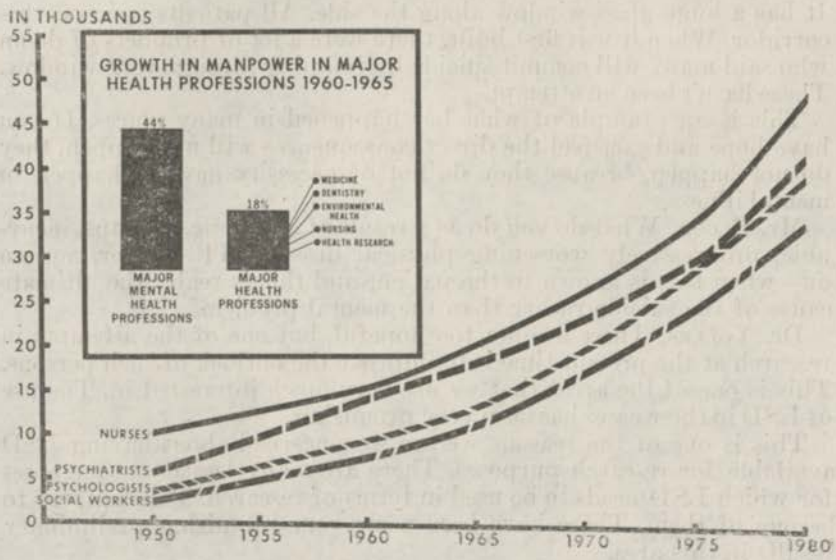
A deliberate decision was made at that time to increase the take from the total medical manpower pool for the field of psychiatry as one example and to increase the number of mental health professionals totally.

It was a deliberate attempt to build up the field. Certain projections were made at that time of how much money it would take over the years to do so. We have had rather generous support from the Congress to increase the number of professionals in the field. This is the result of that support.

Mr. FLOOD. It is working?

Dr. YOLLES. Yes, sir. It is working. We still have a long way to go, however.

TOTAL MANPOWER POOL IN MAJOR MENTAL HEALTH DICIPLINES 1950–1980



The next chart [see facing page] shows the number of community mental health centers that have been funded by year. During 1965, the first year funds were available there were 93. In 1966, 188. We expect by the close of business in fiscal 1967, 286 will be funded.

Mr. SMITH. Are those figures cumulative?

Dr. YOLLES. Yes, sir.

I mentioned the essential services of the community mental health center and I would like to explain them. The basis for the entire community mental health program is the availability of continuity of care to a patient. In other words, the patient's needs are paramount. Depending upon the stage of his illness, his needs will change. We feel that the services available should be at the beck and call of the individual, so to speak, or of his physician, so they can supply the kind of services needed at the time that his illness requires it. Consequently, the program has insisted upon a minimum of five essential services to provide those needs:

Emergency care to take care of an individual in acute need. Just as you have emergency care for physical illness, so you should have emergency care available 24 hours a day for emotional disturbances.

Outpatient care for the individual if that is the way he is best treated.

Inpatient care for those episodes when he is best treated in a hospital in his community, generally in a general hospital.

Then as he improves, it may be——

Mr. FLOOD. Do you isolate them in a general hospital?

Dr. YOLLES. No. It may be a separate ward in a general hospital. Wards are generally open today. That is one major improvement in the last 15 years.

Mr. FLOOD. No steel bars on windows or steel doors?

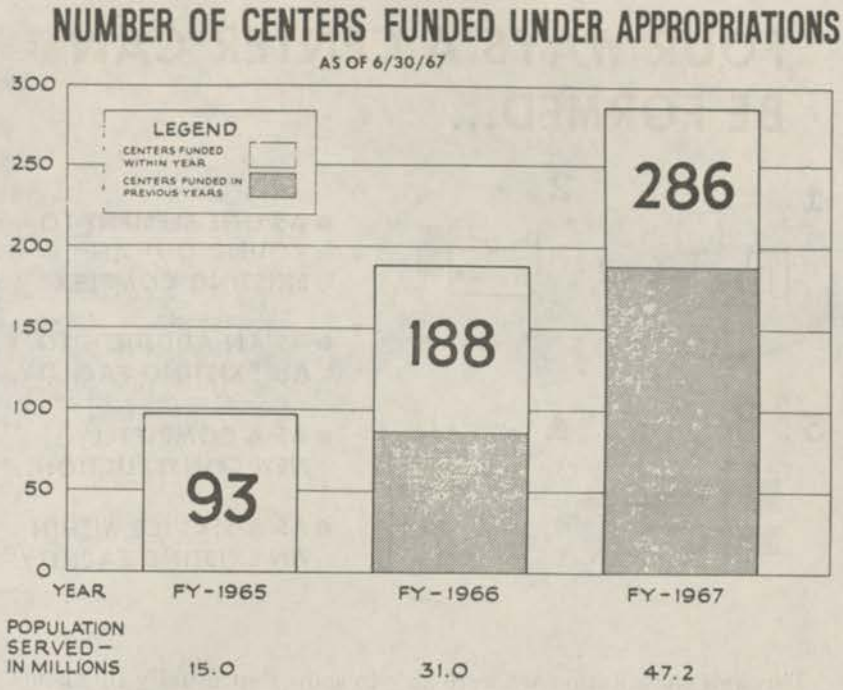
Dr. YOLLES. No, sir. That is a remarkable thing, too. There is a mental health center on the west coast at San Mateo which has a corridor running from the inpatient services to the outpatient services. It has a huge glass window along the side. All patients traverse this corridor. When it was first built, there were a lot of prophets of doom who said many will commit suicide by jumping through that window. There hasn't been an attempt.

This is an example of what has happened in many places. If you have hope and you feel the direct consequences will not happen, they do not happen, because they do not of necessity have to happen in mental illness.

Mr. FLOOD. What do you do as a result of a chronic, perhaps, incurable, progressively worsening physical disease—TB, cancer, and so on—when this is known to the patient and this is really the ultimate cause of the suicide rather than the mental problem?

Dr. YOLLES. These are not too hopeful, but one of the attempts in research at the present time is to improve the outlook of such persons. This is one of the areas that we are very much interested in. The use of LSD in these cases has been very promising.

This is one of the reasons we are so concerned about having LSD available for research purposes. There are many legitimate purposes for which LSD needs to be used in terms of research. This happens to be one of them. There have been some very promising preliminary results in this area.



There are four ways that a center can be formed—as one element to round out an existing complex; as an addition to an existing facility; as a completely new construction; or as a service within an existing facility.

Mr. FLOOD. Who decides that? How do you decide which of the four is desirable in community X?

Dr. YOLLES. This is up to the applicant himself and to the State agency.

Mr. FLOOD. Do you have a power of veto?

Dr. YOLLES. In the construction program, we have less of a veto power. We have not vetoed any State recommendation. But we have sent our consultants out and we have architects and engineers as well to go out and work with these people, both in the development of the application——

Mr. FLOOD. You have no desire or intent to run around with a veto in your hand?

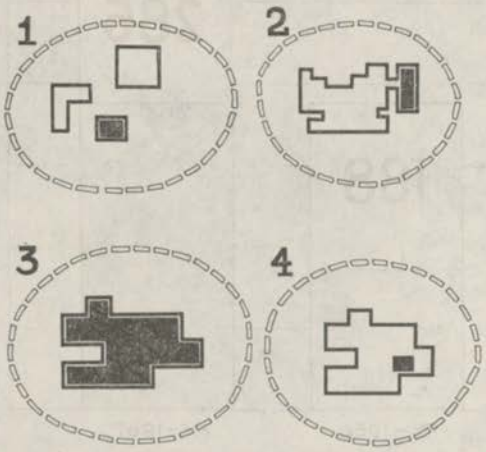
Dr. YOLLES. No, sir. We are concerned with having flexibility in these institutions so they can be converted to newer approaches as they develop. We are certainly concerned not to build any concrete——

Mr. FLOOD. How does the new breed of hospital administrator react to what you are talking about?

Dr. YOLLES. It has been received with a great deal of enthusiasm around the United States. There was initial resistance on the part of hospital administrators in general hospitals, but as we have consulted with them there has been a tremendous amount of enthusiasm.

For example, the old story was rampant that if you put emotionally disturbed patients in a hospital, that means you have to quadruple the number of nurses and have to have 4 policemen to guard them, they make a lot of noise, et cetera.

FOUR WAYS A CENTER CAN BE FORMED...



- AS ONE ELEMENT TO ROUND OUT AN EXISTING COMPLEX.
- AS AN ADDITION TO AN EXISTING FACILITY.
- AS A COMPLETELY NEW CONSTRUCTION.
- AS A SERVICE WITHIN AN EXISTING FACILITY.

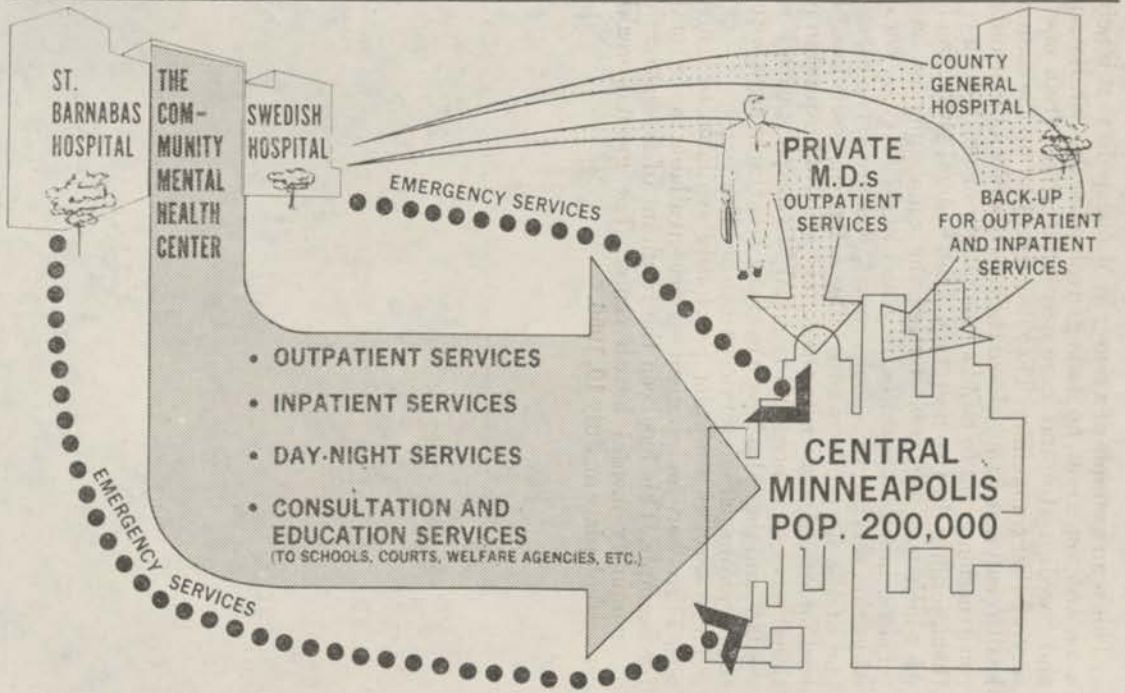
Through consultation we were able to show that usually this is not the case. By allowing some of these persons to visit other installations which have accepted emotionally disturbed patients, they have become advocates of the program rather than resisting.

Mr. FLOOD. If you have six hospitals in town X that get together to do something about this, and it is decided they will build a wing on one of them, they will pick the one, I suppose, not you.

Dr. YOLLES. That is right.

SWEDISH-ST. BARNABAS COMMUNITY MENTAL HEALTH CENTER
MINNEAPOLIS, MINNESOTA

$827,969 FEDERAL SHARE | $1,738,734 TOTAL (INCLUDING LOCAL, PRIVATE FINANCING) | ● PRE-EXISTING EMERGENCY SERVICES | ○ COMMUNITY MENTAL HEALTH CENTER SERVICES | ○ CONTRACTURAL SERVICES | APPROVED - JUNE 27, 1966 | GROUND BREAKING - JULY 10, 1966

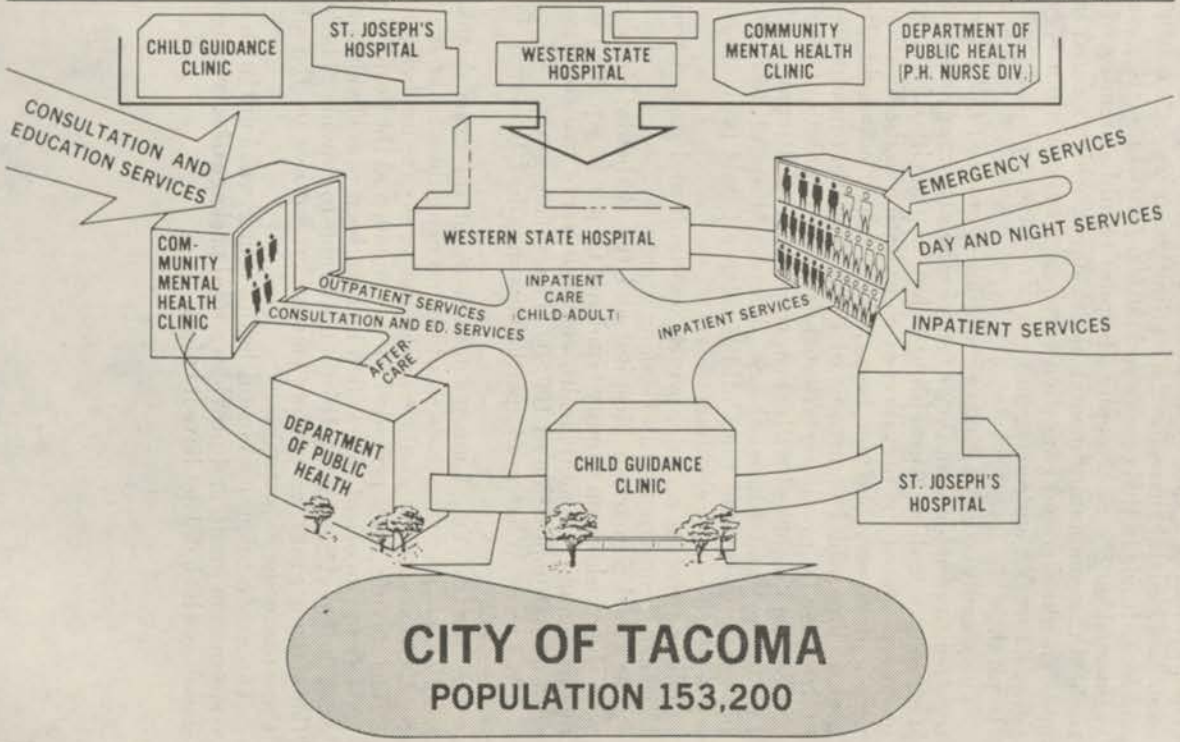


This is an example of a center in Minneapolis that is being built with a construction grant, no staffing involved in this. St. Barnabas Hospital and Swedish Hospital were across the street from one another and serving that community. They decided to set up the community mental health center, and they closed the street between them and applied for a construction grant to build a community mental health center between them, joining the two hospitals. That Federal grant, the Federal share of which was $827,000, enabled the community to have outpatient services, inpatient services, day and night services, consultation and education services to schools, courts, welfare agencies, et cetera. Each one of the hospitals is providing emergency services. They have a backup arrangement with the county general hospital to provide additional services, if needed, to central Minneapolis with a population of 200,000, and they also have a contractual arrangement with local M.D.'s to provide outpatient services when needed.

These services were not previously available to central Minneapolis. There were no inpatient services available to the total population, for example. This has been the resultant of a construction grant for a community mental health center. The ground-breaking for this center took place on July 10, 1966.

TACOMA MENTAL HEALTH CENTER TACOMA, WASHINGTON

FEDERAL SHARE $78,264 | STATE AND LOCAL FUNDS (FIRST 12 MOS.) $180,642



This, in contradistinction, is solely a staffing grant, no construction involved at all. Tacoma Mental Health Center, Tacoma, Wash., serves the city of Tacoma, with a population of 153,000.

There were five agencies operating independently in this area, Tacoma, providing a variety of services, but there was no continuity of care. The Federal share for the staffing grant was $78,000. The State and local funds in this case were $180,000 for the first 12 months. The grant enabled the St. Joseph's Hospital to add a number of staff. If enabled the community mental health clinic, which existed before, to add consultation and education services. Day and night services, inpatient services and emergency services were added at St. Joseph's Hospital.

The stimulus of this staffing grant brought all of these five agencies together to provide a totality of services which was greater than all of them singly had been providing before to the city of Tacoma. The grant stimulated the provision of consultation and education services which previously had not been provided by the community mental health clinic; the Department of Public Health, through its Division of Nursing, is providing aftercare to this population. The Western State Hospital joined with them to provide additional inpatient care for children and adults; the St. Joseph's Hospital now provides inpatient services; and the Child Guidance Clinic provides care on an outpatient basis for children.

This represents a center which was built and staffed with a combination of construction and staffing grants.

The Good Samaritan Hospital and the Bethesda Hospital joined with the Muskingum County Guidance Center [see p. 852] to set up a new community mental health center to serve five counties in Ohio with a total population of 169,800. The staffing grant——

Mr. FLOOD. What would be the area in miles? It is right in the center, is it not?

Dr. YOLLES. Yes. I am not quite sure of the exact distances. Certainly we expect that there would be no more than an hour's travel by road. Otherwise, we would consider the services as not being accessible.

The staffing grant provided for personnel, and the hospital provided 12 beds for inpatient care which had not been provided before. In this case, the Good Samaritan Hospital was able to provide 24 beds through the staffing grant, as well as emergency services by the addition of three professional personnel.

The new community mental health center was built with a Federal construction grant, and provides a total package of service to these five counties which did not have it before.

Mr. SMITH. When they put together a plan like this, they leave a small corridor down at the bottom without service. What possibility is there that those people will ever have this service available, or do you try to encourage them not to leave a little place like that?

Dr. YOLLES. I think this is the area of Cincinnati.

Mr. SMITH. You do try to get them to select a territory which would not leave a small area unserved.

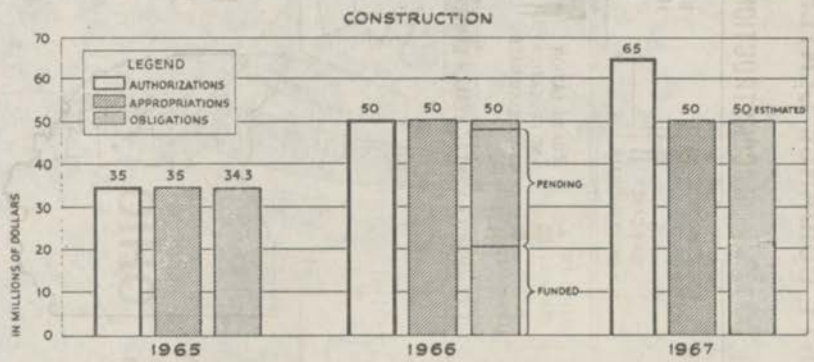
Dr. YOLLES. Before we approved any specific application, the State must submit a plan for the provision of community mental health services throughout the entire State so as to assure that there is effective distribution.

Mr. SMITH. You would not leave some area uncovered?

Dr. YOLLES. No, sir. The State assigns priorities to the filling of the areas within in the State.

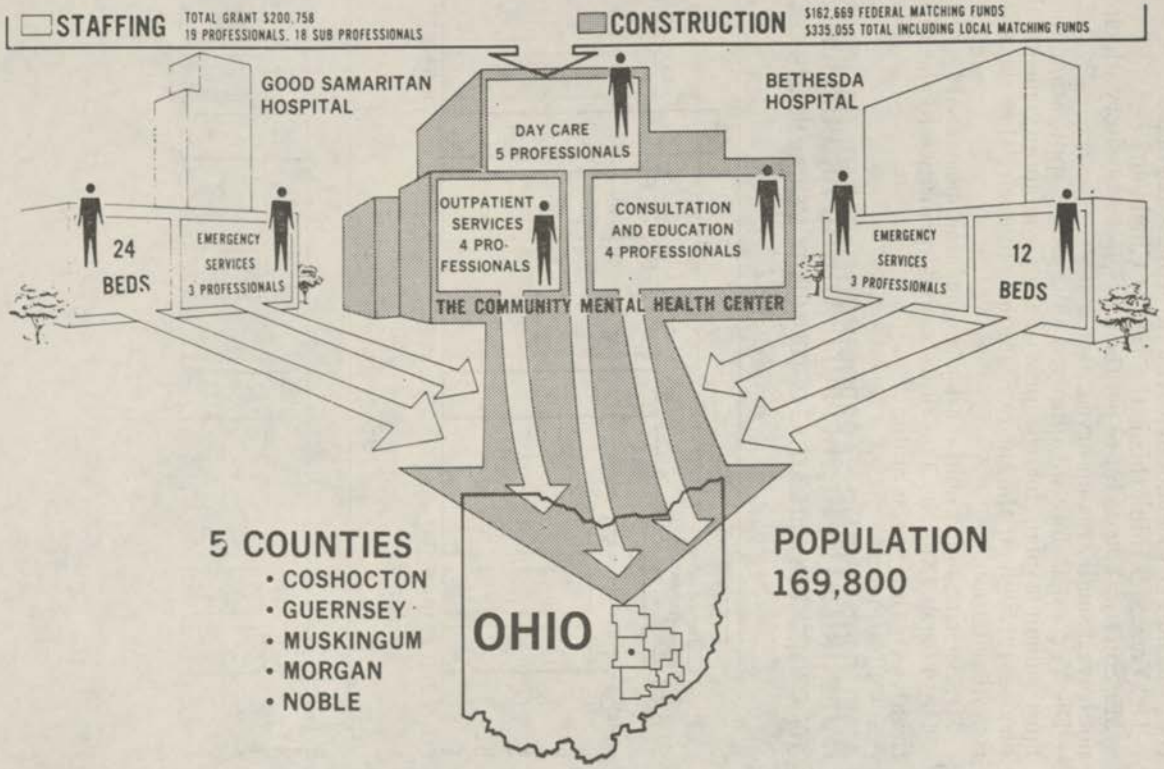
AUTHORIZATIONS, APPROPRIATIONS AND OBLIGATIONS

FOR CONSTRUCTION AND STAFFING OF COMMUNITY MENTAL HEALTH CENTERS



* EXPECTED EXCESS

MUSKINGUM COUNTY GUIDANCE CENTER ZANESVILLE, OHIO



This reflects the authorizations, appropriations, and obligations of the community mental health center program, the graph at the top representing the construction program and the bottom one the staffing program.

In 1965, $35 million was authorized and appropriated for construction and we obligated $34.3 million of the total appropriation.

Mr. FLOOD. You are not going to let these people build a lot of Taj Mahals all over the country, are you?

Dr. YOLLES. No, sir; we hope that they do not build any Taj Mahals, and we hope even more than they do not build these concrete fortresses for the incarceration of the mentally ill. This is the problem we have been wrestling with in the United States. This country has a tremendous investment in real estate. We have buildings which we call State hospitals that in many cases can only be demolished by dynamite. They are not suitably used for anything else. They are not even suitable for the treatment of the mentally ill.

In 1966, $50 million was authorized and appropriated. We expect that these 2-year funds which are available until the close of this fiscal year will be completely obligated.

In 1967, $65 million was authorized and $50 million appropriated, and again we estimate, on the basis of applications which we know to be in hand or in our regional offices, that we will be able to obligate the total amount.

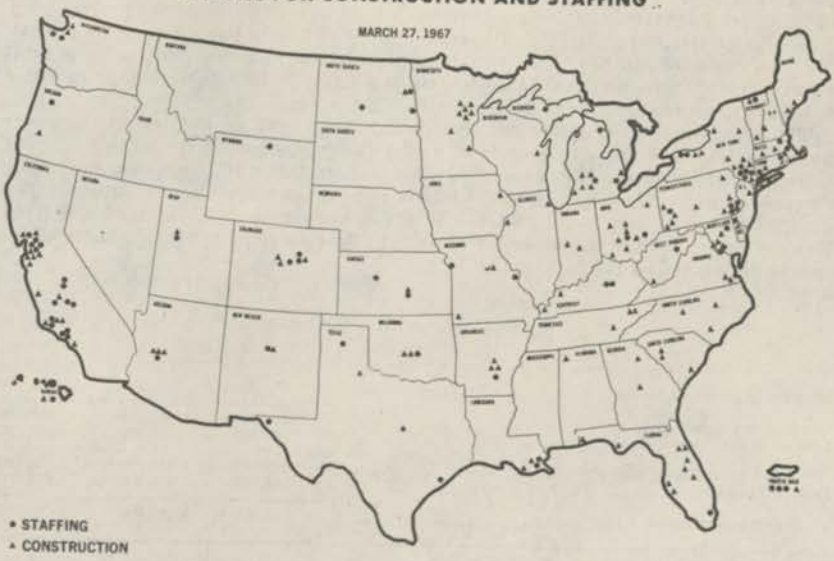
In staffing, $19.5 million was authorized in 1966 and $19.1 million was appropriated. In the latter 4 months of the year $15.2 million was obligated. The funds were available to us for only 4 months because of the lateness of the appropriation.

In 1967, $24 million was authorized; $19.1 million was appropriated; and we have applications in hand totaling to 104 percent of the funds available. There are applications pending to cover 104 percent of the funds, or $22.1 million.

Of the 1968 funds for staffing, $30 million is authorized; $19.9 million is being requested; and we estimate $19.9 million utilization.

COMMUNITY MENTAL HEALTH CENTER GRANTS FOR CONSTRUCTION AND STAFFING

MARCH 27, 1967



• STAFFING
▲ CONSTRUCTION

The last chart is a map representing the distribution of community mental health centers around the United States. You will notice that there is a very good distribution across the United States.

Mr. FLOOD. A good show. McNamara couldn't have done better.

I do not want to monopolize the hearing, but I must get some of this in the record.

SUMMARY OF BUDGET REQUEST FOR MENTAL HEALTH

The adjusted appropriation for 1967 was $227,374,000. The request for 1968 is $248,472,000, an increase of $21,098,000.

ANNUALIZED POSITIONS

The first item of increase is $1,256,000 for what you call "annualization of positions new in 1967." I see no explanation in the justifications. There is no explanation at all, not even of the number of positions involved.

Mr. SADESKY. There are 218 positions for which annualization is requested in 1968. Twenty-nine of these were increases in the President's 1967 budget and there are 189 positions in the 1967 supplemental budget for the narcotic addict rehabilitation program.

Mr. FLOOD. Do you have that anyplace in the justifications?

Mr. SADESKY. No, sir. I do not think we have mentioned the numbers.

Mr. FLOOD. Do you not think you should? Almost everybody else does.

Mr. SADESKY. Yes, sir; I agree that it would be appropriate.

Mr. FLOOD. Will you put in the record some kind of comparatively simple statement to show how you calculated that?

Mr. SADESKY. I will prepare a statement for the record on that.

Mr. FLOOD. After this, mention the number of people. We want to know about that.

(The information follows:)

Annualization costs provide the increase required for full year funding of positions budgeted for only a part of the prior fiscal year. In 1967 there is a total of 218 new positions (29 for continuing NIMH activities and 189 for the new Narcotic Addict Rehabilitation Program) for which only part year (25%) funding was requested in the 1967 regular appropriation and the 1967 Supplemental appropriation. The requested increase of $1,256,000 in 1968 is necessary in order to utilize these positions for a greater part of the year.

The annualization requirement is calculated by first accumulating the gross annual salary and the personnel benefits for the positions involved. This amount is reduced to account for lapses, due to anticipated staff turnover and other factors, to determine the net annual 1968 requirement for these positions. The amount budgeted for these positions in the prior year (1967) is deducted from this net annual figure to determine the annualization requirement. This calculation is illustrated by the following:

	Continuing programs	NARA	Total
Number of positions	29	189	218
Gross annual salary	$246,386	$1,835,314	$2,081,700
Less estimated lapse	23,386	186,314	209,700
Net annual requirement	223,000	1,649,000	1,872,000
Less 1967 funding	148,000	468,000	616,000
1968 annualization	75,000	1,181,000	1,256,000

COORDINATION OF ACTIVITIES WITH THE INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. FLOOD. Last year in the report, you remember, we expressed some disappointment at the apparent lack of sufficient coordination of the activities of your Institute and those of the Institute of Child Health and Human Development especially in the behavioral sciences and the intellectual development of the child.

Did you read the report, or do you bother reading these reports?

Dr. YOLLES. Yes, I read the report.

Mr. FLOOD. If you did read the report, what did you do about it?

Dr. YOLLES. A report on this subject was submitted to the committee. This was prepared by Dr. Shannon of NIH. We were part of NIH at that time.

I may say briefly for the record that we have been working closely with the National Institute of Child Health and Human Development, especially in the area of mental retardation. Our scientists are working with theirs in terms of conferences and discussing new approaches. As yet no particular joint intramural project has eventuated. I am certain if one did come about, there would be no problem having the two Institutes work together.

Mr. FLOOD. We will place the report you mentioned in the record.

(The report follows:)

NATIONAL INSTITUTE OF MENTAL HEALTH, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

REPORT TO HOUSE APPROPRIATIONS COMMITTEE ON THE EMOTIONAL AND INTELLECTUAL DEVELOPMENT OF THE CHILD—JOINT PROPOSAL FROM NIMH AND NICHD, MARCH 24, 1967

The House Appropriations Committee Report No. 1464, on the Department of Health, Education, and Welfare Appropriations for Fiscal Year 1967, requested the National Institute of Child Health and Human Development, and the National Institute of Mental Health to supply a statement showing how these Institutes undertake combined activities of common interest in the field of the emotional and intellectual development of the child and, conversely, where such combined activities are inappropriate.

The 87th Congress established the National Institute of Child Health and Human Development with the mandate to promote studies directed at the entire life process rather than toward specific diseases or illnesses. The program of the Institute would encompass studies of the process of maturation including physical, intellectual and social development with emphasis on the behavioral aspects and on normal development. Up until that time the conduct and support of research in most of these areas had been the responsibility of the National Institute of Mental Health.

The NIMH since its inception has not been disease-limited in its program, and, throughout its existence has placed a positive emphasis on mental health. The creation of an additional resource for the support of developmental research was welcomed, since the present state of knowledge is quite meager.

In order to best exploit this new opportunity, the responsibilities of the two Institutes were defined to avoid duplication and to provide for strong program development in each Institute.

A satisfactory division of responsibilities has been achieved, including such collaboration in common fields of interest that seems appropriate. Initially the NIMH transferred 172 grants totaling $3,000,000 to the NICHD. NIMH scientists participated in NICHD conferences designed to outline the range of NICHD program responsiblities. Currently, visiting scientists with interests in psychological and emotional aspects of development are generally seen by scientist administrators and program specialists from both Institutes in attempts to determine where their interests lie under existing guidelines. Where clear distinctions can-

not be made, requests for support are reviewed by both Institutes, and staff negotiations are held to determine ultimate support.

Further, in one area of particular concern to both Institutes, i.e., mental retardation, a staff group has been established so that the various Institutes can coordinate and collaborate their activities in an effective manner. One of the outgrowths of this committee is a series of seven conferences on various aspects of mental retardation which will be completed during the next several years. The first conference, The Prevention of Mental Retardation through the Control of Infectious Diseases, held in June 1966, was funded by the NICHD. The second, Drugs and Poisons as Etiologic Agents in Mental Retardation, was held February 1967 and funded by the NINDB. The third conference in this series, Socio-Cultural Determinants of Mental Retardation, is planned for April 1968 and will be funded by the NIMH.

General guidelines have been developed to delineate the respective responsibilities of the two Institutes so as to provide an effective working relationship. These current guidelines reflecting the major interests of the two Institutes are as follows:

First, the NICHD is more closely identified with investigations into the emotional and intellectual development of the normal child, while the NIMH is more closely identified with investigations into development as related to the emergence of abnormal behavior, or mental or emotional illness. Its studies of normals are for baseline purposes and comparisons essential for the interpretation of abnormal patterns.

Second, the research programs of NICHD are more closely identified with the development of the child physiologically, intellectually, emotionally, and socially, while the research and service programs of the NIMH are more closely identified with deviations and distortions of development in children who display pathological behavioral patterns.

In three research areas in which both NIMH and NICHD are interested, the separate interests of each have been carefully defined, through the joint efforts of both organizations. These:

Mental retardation

NICHD.—The National Institute of Child Health and Human Development has primary responsibility for research in the biological, behavioral, and social aspects of mental retardation within the context of child health and human development. This includes basic, applied, and clinical research in both humans and animals with respect to etiology, prevention, epidemiology, pathogenesis, diagnosis, and treatment, except for investigations concerned primarily with the central nervous system or mental health and psychiatric disorders.

NIMH.—The research interests of the National Institute of Mental Health are in the mental health and psychiatric aspects of mental retardation. Within this context, the NIMH is concerned with both basic and applied research on the effects of cultural deprivation of children; mental illness growing out of the life experiences of the retarded and its treatment; and in the area of learning, with primary interest devoted to learning in psychologically disordered states and with secondary interest in normative states.

Cultural deprivation

NICHD.—The NICHD has a principal interest in (a) the effect of conditions of life upon physical and intellectual growth—all of the factors associated with normal growth and development, including diet and other factors known to be related to normal physical development; (b) the incidence of disease, as well as the results and residual disabilities that occur; (c) the child's development of adequacy, his ability to cope with the school and other demanding situations of society, his ability to plan and develop a clear, objective perception of himself and his abilities and potentialities, his ability to plan and develop adequate vocational preparation, and his ability to utilize the variety of community resources available to him; and (d) the NICHD is interested in the effects of cultural deprivation upon the adequacy of parental role with respect to promoting all aspects of the child's welfare—other than those that are primarily the concern of the NIMH—and in personality variability as influenced by cultural deprivation.

NIMH.—In the area of cultural deprivation (as that term refers to severe socio-cultural life deficiencies which affect individual development and adjustment), the NIMH has a principal interest in (a) the effects upon the emotional and psychological development of children caused by the distorting influences of cultural deprivation on mental growth, personality development, the self-

sufficiency of individuals and their ability to cope with the task of developing adequate adult roles; (b) the stressful influences which the disturbed or retarded child's presence generates within the family; (c) psychiatric and emotional disabilities, such as those evidenced by school phobias, neurotic behavior, other evidences of anxiety states, and the lack of parent-child relationships produced by culturally deprived circumstances. The NIMH has a principal interest in interference with the parental role and the resultant psychiatric or emotional disorders. Finally, the NIMH has a primary interest in deviant and abnormal patterns of personality development.

Learning

NICHD.—In the area of learning, the NICHD has primary interest in normative states and in the problem of intellectual and cognitive differences of development at various age levels. Studies will include the molecular and biochemical factors in learning, the effect of cutural deprivation on learning, the effect of brain damage and perceptual and sensory disorders on learning disability and methods for remediation, and the health and related aspects of learning impairment.

NIMH.—In the area of learning, the NIMH has a primary interest in learning in psychologically disordered states, and a secondary interest in learning in normative states. This includes the study of the relationship between learning and the personality and social and emotional development of the child; the effects of learning deficits on the child's personal and social adjustment (e.g., his failure to achieve minimal levels of social competence of adequate adaptive behavior); the impact of early childhood deprivation or early emotional disturbance on learning; the relationship between learning factors, such as attention, acquisition, retention, motivation, application, and the rate and level of mental development, especially as the latter influences the adequacy of personal and social adaptive behavior.

Similarly, joint statements of interest in certain areas have been worked out by the NICHD and the NIMH.

Mental retardation

The NIMH and the NICHD share a joint interest in research studies of epidemiology, etiology, diagnosis, placement, and treatment in the area of mental retardation.

Learning

The NICHD is concerned with the problem of intellectual development of the child, and, therefore, in the basic and generic problem of learning at all stages of childhood. The NIMH has an interest in the failure to achieve normal rates of learning or competence and the development of distorted patterns of behavior that can be understood only in terms of learning effects.

Personality development

The NIMH is interested primarily in deviant and abnormal patterns, and in the factors involved in and the nature of variations of personality development which are relevant to mental health and illness.

The NICHD also will be interested in personality variability as it relates to normal child development.

Given these similarities and differences in the interests of NIMH and NICHD in the emotional and intellectual development of the child, it is both desirable and feasible that the two organizations undertake certain combined enterprises.

The differences between the research approaches of the NICHD and the NIMH can be highlighted and complemented with research undertaken as a combined enterprise. Thus, abnormal behavior patterns are more sharply brought into focus when displayed against a background of normal behavior patterns, and conversely, that which is normal can frequently be best understood only in relation to that which is abnormal.

Similarities of research approaches of the NICHD and the NIMH may make it possible for the two organizations to develop research using the same facilities and the same subjects of population groups, but utilizing these facilities and subjects in ways unique to each organization.

Thus, the NIMH has been involved in studies within the NICHD's Mental Retardation Children's Diagnostic and Study Unit at the National Naval Medical Center, and opportunities exist for cooperation in the studies of aging being undertaken at the Gerontology Branch Laboratories in Baltimore.

As the intramural research program of the NICHD develops further, there will be occasions when the complementary interests and skills of the investigators in the two organizations will develop joint projects which neither could pursue as powerfully without the participation of the other group.

The addition of NICHD staff and research approaches to certain studies being undertaken by NIMH's laboratories at the National Institutes of Health could contribute much to both the NICHD and the NIMH.

To conclude, *it is evident that in the short span of time since the NICHD was established, the NIMH and the NICHD have done much to identify both their joint and separate interests in the problems of the emotional and intellectual development of the child. Given this sound beginning, it is possible to assume that carefully selected joint enterprises, undertaken in the future, will enrich the research activities of both organizations.*

Mental Health Training and Manpower

Mr. Flood. You also will recall that we said, "The committee expects at the 1968 hearings a fresh assessment of the requirements for mental health personnel."

Well, these are the 1968 hearings.

Dr. Yolles. We have prepared a report which we submit for the record.

Mr. Flood. The witness shows me a report entitled "Mental Health Training and Manpower, 1968–72," U.S. Department of Health, Education, and Welfare, Public Health Service, with a foreword by Dr. Yolles, the Director, who is now in the witness chair. We will at the proper place put this report in the record, since we asked for it. You might hit the high spots for us.

Dr. Yolles. In terms of the preparation of manpower, as I indicated before, there is a need for a vastly increased number of personnel in the mental health field. Let me give one or two examples of the need for personnel.

Among the Veterans' Administration hospitals and State hospitals for the mentally ill and mentally retarded, about one out every four budgeted positions for staff psychiatrists is unfilled. If you compare the number of situations wanted each month to the total positions offered, the relationship is 1 to 23. There are 23 jobs available for every one person looking for a job in the area of psychiatry.

One out of five budgeted positions for professional registered nurses in non-Federal psychiatric hospitals was unfilled in June of 1965.

Sixteen percent of budgeted positions for social workers with mental health training are unfilled in the States.

I might point out that only 6 percent of all physicians and only 3 percent of all nurses have had some psychiatric training or experience.

In the face of these vast needs, we must develop and continue to develop a very active, ongoing program for the development of manpower.

We have indicated in the report that there are certain funds that would have to be appropriated in order to continue to expand the support of training activities throughout the United States. I might point out, too, that when the Institute started, years ago, there were only a handful of departments of psychiatry that could be really called so in the United States; but with the development of the training program of the National Institute of Mental Health and with the support and encouragement of the Congress, we have expanded our efforts in the field of training of mental health professionals so that now

every medical school in the United States has a first-class department of psychiatry.

Mr. FLOOD. Can we streamline the years of study, take a year or two off that?

Dr. YOLLES. I would hope we could get to that point. There have been a number of efforts made to streamline the entire medical curriculum, for example.

Let me point out that we have a special program which was organized last year with the reorganization of the Institute, whereby we are trying to develop new approaches to the training of mental health professionals. This will be an experimental program trying to shorten and change the approaches to the training of mental health professionals.

We can expect on the basis of the projections for coming years—which we made in 1962, and we have not been far off in our projections—that with an annual increase of about $15 million in appropriations for training grants these programs of support for personnel in the mental health field will continue to grow appropriately. With such support, as I pointed out before we will be able to reach our projected goals in numbers of personnel needed by 1980 to take care of the 2,200 community mental health centers, the needs of research, the needs of hospitals, the needs of training, and the needs even of the private practice of psychiatry in the United States. This is true as well for the other professions in the mental health field.

If I may summarize, there are new and experimental approaches needed. There is need for support of the training and refresher courses for medical personnel and mental health professionals already out in the field, and continued support on the projected basis for the development of mental health personnel over the years.

(The formal report follows:)

MENTAL HEALTH TRAINING AND MANPOWER 1968–1972

FORWARD

This document has been prepared in response to a request by the House of Representatives Committee on Appropriations for an assessment of the requirements for mental health personnel for the next five years. Examination of the document will reveal the dramatic growth that has occurred in the National Institute of Mental Health training program since its inception in 1948. Especially during the past five years there has been marked increase in the sheer numbers of mental health personnel and in the capacity of the training centers to produce this manpower. Of equal significance is the fact that there has also been significant improvement in the quality of the Nation's training programs and a generalized responsiveness to the needs for training programs and a generalized responsiveness to the needs for training to meet new demands for service, research, administration and teaching.

In additon to support of the categorical mental health disciplines, programs have been initiated in a number of special and experimental areas. There are now continuing developments in new areas, especially community mental health, to produce personnel to meet the challenge of the national mental health program. To meet this goal it will be necessary to increase the size of the training program so that the present mental health manpower pool of almost 68,000 psychiatrists, psychologists, social workers and nurses, increases to over 99,000 by 1972. In addition, there is also an immediate requirement for strengthening and enlarging the total manpower supply in mental health through innovative and imaginative development of new manpower sources.

The programmatic growth and future objectives described in this document serve to emphasize the need for maintaining the rate of growth already demon-

strated. Only by providing the manpower resources required can we hope to achieve the goals of the national mental health program.

STANLEY F. YOLLES, M. D.
Director, National Institute of Mental Health.

I. BACKGROUND AND DESCRIPTION OF PRESENT MENTAL HEALTH MANPOWER PROGRAMS

A. Introduction

The House of Representatives Committee on Appropriations in its report on the appropriations bill for fiscal year 1967 for the Departments of Labor and Health, Education, and Welfare, once again expressed its deep concern over the longstanding and continued critical shortage of trained manpower in the mental health fields. In response, the NIMH has prepared this comprehensive report on the requirements for mental health personnel, by professional and sub-professional categories, for the next five years, including estimates of the funds required, and a plan for meeting these requirements.

It should be emphasized that the estimates of funds needed in 1968 through 1972 represent a professional judgment and are not reflected in official budget presentations.

B. The Present Manpower Supply

Concern is being expressed from so many different quarters regarding general manpower shortages in the Nation that the point hardly needs to be belabored. The rapid advances in technology and the growth and changes in the population have led to an especially urgent demand for greater numbers of highly skilled persons in all fields. Emphasis is being placed simultaneously upon consideration of methods for increasing the supply of such personnel and improving the utilization of available manpower.

In 1961 the Institute initiated a mental health manpower studies program which has been coordinated with the overall manpower activities of the NIH and other PHS components, and has utilized, to the maximum possible extent, existing sources and mechanisms for the collection of manpower data. Highest priority has been given to the assessment of manpower requirements in the light of changing patterns of mental health service, teaching, and research activities. The program places considerable emphasis upon close collaboration with the professional societies in the mental health field, such as the American Nurses Association, American Psychiatric Association, American Psychological Association, Council on Social Work Education, National Association of Social Workers, and the National League for Nursing.

Delineating the manpower situation in the area of mental health is inherently and immediately more difficult than in other segments of the health manpower field, because it is difficult to circumscribe, define, or identify the concepts of "mental health" and "mental illness," unlike the situation in other health areas anchored to clear-cut disease entities or organic disorders. There are, therefore, of necessity somewhat arbitrary and changing boundaries regarding the professional and technical workers to be included in the mental health manpower pool. It is generally considered that the major professional fields, the "core" groups, are psychiatric nursing, psychiatry, psychology, and social work. As the needs in mental health become more comprehensive and as the efforts to improve mental health become more extensive, however, an increasing number of other professional groups are becoming more important to services and research in mental health. Such professions as occupational therapy, teaching, the clergy, and research scientists in the biological and social sciences are all making contributions. In addition, other workers such as psychiatric aides and nurse attendants provide all-important services. Re-evaluation of traditional roles and functions, and innovative training approaches are leading to the development of new types of mental health workers to further add to the trained manpower pool.

1. Growth in the four core areas

Specifically within the four core areas there has been growth over the past five years in total numbers of professional personnel. Counting only those persons within the four core disciplines, Table 1 provides figures for 1960 and 1965.

TABLE 1.—*Growth in numbers of psychiatrists, clinical psychologists, psychiatric social workers, and psychiatric nurses, 1960–65*

	1960	1965
Psychiatrists	13,000	18,750
Psychologists	9,000	13,265
Social workers	7,200	11,378
Nurses	15,000	20,554
Total	44,200	63,947

The 1965 figures represent an increase of 44 percent over the 1960 total. This increase in the core mental health professions is in considerable contrast to a 19-percent increase in five major health professions (medicine, dentistry, nursing, environmental health, and health research) between 1960 and 1965.[1] While impressive it should not be a cause for complacency. The increase reflects the acute manpower shortages that have existed in mental health. The baseline was so low that the increases have not yet been sufficient to eradicate the gap. All indications at present point to a continued manpower shortage if the existing rate of output of professional personnel does not increase. In 1966 APA reported that the *rate of improvement* in the ratio of professional personnel[2] to patients in public mental hospitals was declining: that is, between 1960 and 1962 the ratio improved by 13 percent; from 1962 to 1964 there was an increment of 11 percent.[3]

Despite the marked increases that have occurred between 1960 and 1965 in the mental health professions, the 1961 statement of the Joint Commission on Mental Illness and Health still applies: ". . . sufficient professional personnel to eliminate the glaring deficiencies in our care of mental patients will never become available if the present population trend continues without commensurate increase in the recruitment and training of mental health manpower. The only possibilities for changing this negative outlook for hundreds of thousands of mental hospital patients would require a great change in our social attitudes, and a consequent massive national effort in all areas of education, including large increases in the number of persons engaged in mental health work, or a sharp break-through in mental health research."[4]

The documentation of the long-standing manpower shortages via numerical enumeration is valuable in its own right, yet it presents only a partial picture of the total situation. As new concepts of treatment, research, and teaching in the field of mental health emerge, need for additional personnel becomes even more acute since these new concepts and findings require trained persons as the vehicles for their implementation. However, increased knowledge and experience, while creating increased demand on the major traditional disciplines, have also highlighted the role of groups such as the hospital aide and the occupational therapist. This is a reflection of the ever-increasing trend away from custodial hospital care to a more dynamic treatment model.

The Community Mental Health Center has occasioned a reevaluation of the entire societal concept of mental health and illness and a corresponding creation of new types of mental health workers trained in new and innovative ways. Further, as our society moves to attack its total range of ills such as poverty and the killer diseases, and to increase and upgrade its educational endeavors, the mental health professional becomes in ever-increasing demand. While these problems are not the primary domain of the mental health professions, they do involve human behavior. A voluminous body of research literature attests to the relevance of mental health concepts, findings, and teaching to all these areas. Consequently, the psychiatrist, psychologist, social worker, and nurse are increasingly needed for their consultative skills by the agencies and professionals who are responsible for these other efforts.

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[1] Based on 1960 figures in *Health Manpower Source Book, Section 18: Manpower in the 1960's*, Washington, D.C.: DHEW, PHS, Division of Public Health Methods, 1964, Table 9, p. 15, and 1965 estimates for the total in the five fields provided by Maryland Y. Pennell.

[2] Includes physicians, psychologists, psychometrists, psychiatric and other social workers, registered nurses, occupational and other therapists.

[3] Joint Information Service. *Fifteen Indices*. Washington, D.C.: American Psychiatric Association, 1966, p. 12.

[4] Joint Commission on Mental Illness and Health. *Action for Mental Health*. Science Editions, Inc., New York: 1961, pp. 140–141.

No segment or level of the mental health manpower pool can be considered to be adequately supplied at present; to attempt to assign priorities to given elements of the pool and ignore others would only create further imbalances and problems. Alleviation of shortages must occur "across the board."

2. Current status and role of the major professional groups

a. *Nursing.*—Nursing is the largest health profession. It is estimated that there are approximately 621,000 active professional nurses practicing in the U.S. at present.[5] A 1963 NIMH manpower survey[6] revealed that about 18,100 nurses are employed in 2,000 mental health establishments.[7] Of these, 3.6 percent, or about 640 nurses had graduate degrees and an additional 9.3 percent (1,680 nurses) had some graduate training. Those with bachelor's degrees constituted 11.4 percent of the group (2,050 nurses). The remainder (74.8 percent) included 12,800 nurses with three-year diplomas and 670 with less than that amount of training. Preliminary data available from a 1965 study by the NIMH not yet published regarding 3,380 nurses employed primarily in psychiatric services of over 2,200 general hospitals show fairly similar proportions falling within each of the above educational categories.

More sharply delineated educational programs for nurses have resulted in a marked shift in the role and function of the nurse from that of custodial care to involvement in preventive, therapeutic, and rehabilitative patient care activities. This is particularly noted as the locus of treatment shifts from the traditional hospital to the comprehensive community mental health center. At a recent work conference on graduate education in psychiatric mental health nursing, the following knowledge and skills were indicated as needed for competent psychiatric nursing practice: 1) a clear concept of health and the dynamics involved in the development and maintenance of a healthy personality; 2) well-formulated concepts of the dynamics involved in the development of illness and in the treatment process; 3) an understanding of the dynamics involved in individual, group, or family interaction, both healthy and pathological; 4) understanding of social and administrative structure and process within mental health facilities as these affect patient progress; and 5) understanding of the roles of other disciplines and agencies involved in the care of the mentally ill and the dynamics of interprofessional relationships, particularly as these affect individuals receiving care.[8]

b. *Psychiatry.*—Between 1960 and 1965, membership in the American Psychiatric Association grew from 11,600 to 14,300. An NIMH-sponsored manpower survey conducted in 1965 by the APA located 18,750 psychiatrists (including residents) of whom 15,200 were estimated to be in active practice.[9] The number of psychiatric residencies offered has increased from 3,838 in 1960 to 5,000 in 1965.

In the past decade, the role and function of the psychiatrist has expanded due to a number of trends in mental health programs, primarily away from custodial care, and toward the closer interrelation of mental health programs with community general health services. Hospitals are providing more inpatient and outpatient services for persons who seek help on a voluntary basis, and a closer relationship is growing between the mental hospital and the community. Hospitals are doing more training. There is an encouraging increase in the interest and activity of psychiatrists in research. Further, many major psychiatric training centers are moving toward strengthening their research programs. Funds for research training in psychiartry are also stimulating this trend. At the same time, insofar as services are concerned, the increase in the relative number of old people and children in the population in general is causing a shift in the hospital and clinic population. The use of new drugs has released more hospital patients into the community and thereby increased the need for follow-up services. Special area such as mental deficiency, juvenile delinquency, and alcoholism are

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[5] Estimated by the Interagency Conference on Nursing Staistics, cited in *Facts about Nursing*, New York: American Nurses Association, 1966, p. 7.

[6] *Selected Characteristics of Nurses Employed in Mental Health Establishments, 1963.* Mental Health Manpower Current Statistical and Activities Report No. 7, Washington, D. C.: DHEW, PHS, NIMH.

[7] These included out-patient clinics, hospitals for the mentally ill, and institutions for the mentally retarded. Federally supported establishments such as Veterans Administration and PHS facilities were not included.

[8] University of Pittsburgh School of Nursing, Department of Psychiatric Nursing. *Report of Work Conference in Graduate Education in Psychiatric-Mental Health Nursing.* Pittsburgh: 1964.

[9] *Occupational and Personal Characteristics of Psychiatrists in the United States, 1965.* Mental Health Manpower Current Statistical and Activities Report No. 9, Washington, D.C.: DHEW, PHS, NIMH.

receiving increased attention and professional service. Child, preventive, social, and industrial psychiatry are all areas of professional activity which have expanded over the past decade.

c. *Psychology.*—Since World War II, there has been a marked growth in the applied areas of psychology, particularly those concerned with mental health. The latter group, however, is not as clear-cut as the identification of psychiatric nurses or psychiatrists. While clinical psychologists are clearly within the mental health field, there are other areas within psychology that relate to mental health. The 1964 National Science Foundation Register survey of psychologists revealed that 69 percent of the 16,800 responding considered their work to be relevant to mental health.[10]

Insofar as total membership of the American Psychological Association is concerned, there were 18,215 members in 1960 and 23,561 members in 1965.

Of all the mental health professions, psychology and psychologists continue to be the most active in research. Data from the 1964 National Science Foundation Register reveal that 24 percent of the psychologists responding consider their most important job activity to be research.[11] The greatest proportion of research in mental health is conducted by psychologists. In addition, psychologists in the mental health field are active in diagnostic testing, in psychotherapy, in teaching, and training of students, and as is the case with all the mental health professions, the traditional roles and functions are being reevaluated and expanded, particularly to encompass the new community mental health concepts into both research and service endeavors.

d. *Social work.*—In the most recent comprehensive study of social welfare manpower in the United States, conducted by the Bureau of Labor Statistics in 1960, it was estimated that there were approximately 116,000 social welfare personnel. The Department of Labor estimated that in 1963–64 there were not less than 125,000 persons providing social work services in voluntary and public agencies, of whom approximately 25 percent were graduates of schools of social work, and 75 percent were trained in agency inservice programs.[12] In social work, as in psychology, it is as difficult to confine the mental health contribution to the psychiatric social worker as it is to the clinical psychologist alone. A recent change in the graduate social work curriculum to a single generic approach makes the distinction between psychiatric social work and the rest of social work even less clear than in the past. Nonetheless, it is possible to identify those social workers who are employed in psychiatric specialization.

The 1963 NIMH survey of professional personnel in mental health establishments estimated that about 7,500 persons identified as social workers were employed in the 2,000 institutions surveyed.[13] The establishments studied were hospitals for the mentally ill, institutions for the retarded, and outpatient psychiatric clinics. Of the social workers surveyed, 74 percent had master's degrees, 13 percent had graduate study but no degree, and 11 percent had bachelor's degrees or less. The 2,200 general hospitals surveyed in an as yet unpublished study revealed that 660 social workers spent the majority of their time in care of the patients in psychiatric units.

A recent report on social work manpower problems defines social work as ". . . the system of organized activities carried on by a person with a particular knowledge, competence, and values, designed to help individuals, groups or communities toward a mutual adjustment between themselves and their social environment. The goal of social work is the enhancement or restoration of the capacity for social functioning of individuals or groups, or the development of community conditions that support social welfare, through counselling, the provision of services, or community organization activities." [14]

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[10] Jones, Donald R. *Psychologists in Mental Health 1964.* Washington, D.C.: DHEW, PHS, NIMH (In press).

[11] *Reviews of Data on Science Resources.* Vol. 1, No. 2, Dec. 1964, National Science Foundation, Washington, D.C.

[12] *Employment Outlook for Social Workers,* Bulletin No. 1375–43, Washington, D.C.: U.S. Department of Labor.

[13] *Selected Characteristics of Social Workers,* Mental Health Manpower Current Statistical and Activities Report No. 6, Washington, D.C.: DHEW, PHS, NIMH.

[14] *Closing the Gap in Social Work Manpower: Report of the Departmental Task Force on Social Work Education and Manpower.* Washington, D.C.: DHEW, Office of the Under Secretary, 1966.

3. Other professional and subprofessional groups in mental health

a. *Research personnel in the biological, behavioral, and social sciences.*—Increasingly, within the past decade, major contributions to mental health research are being made by sociologists, pharmacologists, anthropologists, biochemists, and other research workers in related fields. In social sciences, the period following World War II is considered to be the point in time when work accelerated noticeably on the relationship between social factors and the prevention and treatment of mental illness. Not only sociology, but anthropology, political science, and economics have contributed distinctively to mental-health-relevant literature.

Sociologists, for instance, are studying the ecology and epidemiology of mental illness and the therapeutic milieu in the mental hospital. Anthropologists have been studying primitive and modern societies to determine cultural concomitants of mental illness.

Mental health economics, including study of the costs to society and the patient, the relationships between economic variables and such problem areas as suicide and delinquency, is an area in which research is beginning to make significant contributions. Urban planning, the interrelationships of personality and politics, decision-making, and study of public policy as they relate to mental health are topics on which political scientists are now working.

Each of these disciplines is notably short of manpower for purposes of conducting such research. An additional demand upon the supply of social scientists has developed in the last decade, with the growing emphasis upon inclusion of behavorial and social science content in medical education. The recent Coggeshall report on medical education demonstrates quite conclusively the need for the modern physician to be grounded in the concepts of the behavioral and social sciences.[15] The 1964 NSF register of sociologists contains data on 2,700 persons. There are probably between 2,000 and 2,500 anthropologists in the country.[16]

In the biological sciences, pharmacologists have played a critical role in the development of new drugs. In the past decade, knowledge of genetics, developmental biology, neurophysiology, stress physiology, and psycho-pharmacology has increased to the point where it has direct impact upon our understanding of human behavior and its disorders. These and other scientists now in short supply generally will become even more important to the mental health field as the research in mental illness continues to extend deeper into basic research in the biological and social sciences.

b. *Psychiatric aides.*—At present over 100,000 persons are employed as psychiatric aides or attendants in psychiatric hospitals. A 1963 NIMH manpower survey revealed that State and county hospitals alone employed over 96,000 psychiatric aides.[17] There is an estimated 25-percent yearly turnover in these personnel. About 90 percent of the 210 hospitals reporting stated that they maintained some type of formal training program for aides. About 40 percent of all aides (based on a sample of over 8,400) have completed high school with 21 percent stating that they possessed only a grade-school education. About two-thirds of all aides earned less than $4,000 per year. Relatively small percentages of aides reported that they spend most of their time in activities associated with psychotherapeutic aspects of patient care. Their duties consisted primarily of minor medical care, protecting the patients' personal belongings, telling the nurse about a patient's physical complaints, encouraging and reassuring the patients, having friendly conversations with patients, and keeping dangerous objects away from patients.

Various efforts have been made in the past to institute training programs and to improve salaries and working conditions. However, the pay is usually quite low as is the status of the aide within the hospital community. In recent years, efforts have been initiated to improve these conditions.

According to a report of the American Hospital Association,[18] aides contributed approximately 82 percent of the full-time nursing personnel in psychiatric institutions in 1957. However, the training programs now existent in the country are not in agreement as to objectives to psychiatric aide education or the characteristics of such training. The training varies from on-the-job training, to short periods of formal training prior to employment, to training programs which

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[15] Coggeshall, L. T. *Planning for Medical Progress Through Education.* Evanston, Ill.: Association of American Medical Colleges, 1965.

[16] Estimate by Dr. Charles Frantz, Executive Secretary, American Anthropological Association.

certify graduates for employment as psychiatric aides. The majority of aides, however, receive no training at all prior to employment and once on the job the need for service apparently takes priority over learning needs.

c. *Occupational therapists.*—Occupational therapists play an important role in the rehabilitation of hospitalized mental patients. As with all health fields today, occupational therapy is undergoing changing concepts and practices. In an important recent conference on education in occupational therapy, a number of recommendations pointed toward the need for increased academic and clinical training in order to prepare the occupational therapist to understand and deal with the psychodynamics of the patient and to enable the therapist to make the most effective use of himself in a therapeutic interpersonal relationship.[19] As efforts at more dynamic hospital treatment develop, this newer role of the occupational therapist will become more important. It is estimated that there are at present over 8,000 occupational therapists.

d. *The clergy.*—A major group to whom people bring their emotional problems, as highlighted by the Joint Commission, is the clergy. The one-third of a million clergy in the United States represent, therefore, an important source for mental health services. Within recent years as a result of recognition of the need for greater understanding of the principles of counselling and current mental health concepts, there has been a sharp increase in requests for training in pastoral psychology. This growing emphasis is true in the three major faiths. The role of the chaplain in the mental hospital has become increasingly actively over the past twenty years.

e. *Consideration of other categories of personnel.*—As the manpower emphasis has shifted to a focus on full utilization with concomitant search for new and innovative approaches to the teaching and utilization of traditional mental health manpower groups, it is natural that consideration also be given to explorations of the use and training of totally new groups of persons.

The past few years have seen considerable creative thought devoted to the mental health training and utilization of persons who are usually referred to as "subprofessionals" who perform a variety of tasks and functions under professional supervision, previously performed only by fully trained professionals. Thus, by careful re-evaluation of professional functions, it becomes increasingly feasible to use persons with high school or college level training in the mental health field and thus free the fully trained professional to devote his efforts to the functions requiring his full range of training and experience. The NIMH is currently supporting training efforts in this experimental area and is carefully evaluating their success and potential for greater use.

In the field of psychology, the emphasis has always been on the doctorate as the minimum for full professional training, although persons with master's degrees do function in a wide range of settings. Psychology has become increasingly interested in the possible broader use of master's-level-trained personnel, realizing the many functions that such persons can perform under supervision, were they provided with adequate training. The NIMH is currently developing a study to assess the training requirements for specific areas of function of such persons to provide the necessary data for further decisions and planning.

Expanded use of subprofessional personnel in no way, of course, provides substitutes for full professional training. It does, however, permit the professional, by providing supervision to such staff, to expand his effectiveness and his services, and to maximally use the skills he possesses. Furthermore, creation of such new roles permits mental health recruitment to draw upon a new labor pool, offering new and meaningful public service employment for interested youth.

C. *The Role of NIMH in Training*

The history of the NIMH training program from 1948 to 1961 has already been documented.[20] The more recent developments and trends, from 1962 to the present have included the inauguration of a program devoted to the inservice training of

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[17] *The Psychiatric Aide in State Mental Hospitals.* Washington, D.C.: DHEW, PHS, NIMH. PHS Publ. No. 1286, 1964.

[18] *Hospitals, Journal of the American Hospital Association*, Part II, Guide Issue, XXXII, No. 15 (August 1, 1958), pp. 402–403, 405. Cited in *A Project in Preservice Psychiatric Aide Education*, The College of Nursing, Wayne State University, Detroit, Michigan: 1960, p. 2.

[19] West, W. L. (Ed.) *Psychiatric Occupational Therapy.* New York: American Occupational Therapy Association, 1959.

[20] Robertson, R. L. and Rubinstein, E. A. *National Institute of Mental Health Training Grant Program, Fiscal Years 1948–1961.* Washington, D.C.: DHEW, PHS, Publ. No. 966.

subprofessional personnel, primarily aides, in State institutions for the mentally ill and mentally retarded. It is hoped ultimately to extend the scope of this program to other categories of agencies and personnel.

A broader approach is also being taken to the problem of maintaining the skills of those mental health professionals already in the active manpower pool. Towards this end the NIMH has recently established support programs for the development of continuing education for all types of mental health manpower. It is hoped to promote the development of divisions within training centers devoted to continuing education. The pressing need for support of this kind has become increasingly evident as the field faces the problem of staffing the comprehensive community centers, which will require techniques and capacities different from those on which traditional education concentrated in the past.

Throughout the history of the training program there has also been research fellowship support, and since 1954 there have been awards to research psychiatrists and scientists in related disciplines to enable them to spend considerable periods of time in full-time research. Originally termed Career Investigator awards, this general type of support is now called the Research Career award.

As a reflection of the recent rapid growth, over two-thirds (71 percent) of more that $450 million awarded from the beginning of the program through fiscal year 1966 was awarded during the last five years. About 1,150 grants were made to support mental health training programs in fiscal year 1962. In fiscal year 1966, almost 2,000 training grants were awarded.

TABLE 2.—*Number and amount of mental health training grants, and average amount per grant, fiscal years 1962–66*

Fiscal year	Number of grants	Total awards	Average amount per grant
1962	1,145	$39,374,975	$34,389
1963	1,333	50,311,927	37,743
1964	1,688	68,952,663	40,849
1965	1,816	75,523,250	41,588
1966	1,972	[1] 86,081,000	43,652
Total, 1962–66	7,954	320,243,815	40,262

[1] Includes $2,278,000 comparative transfer of funds for inservice training in mental retardation.

From about 4,500 graduate traineeships in fiscal year 1962, the training grants program has grown to provide almost 8,200 graduate trainee stipends in fiscal year 1966. In addition, smaller stipends for extracurricular summer and part-time study have been awarded annually for the psychiatric training of several hundred medical students in recent years.

Throughout the five-year period here considered, funds were awarded to provide 32,925 graduate traineeships. This number substantially exceeds the number of individual trainees receiving stipends during this five-year period, since many trainees are supported for a second, third, or subsequent year of training. Among the major mental health disciplines, approximately 5,700 social work students received training. More than 4,600 persons received training in psychology at a graduate level, while about 5,000 physicians received residency, research, or other types of training in psychiatry. Some 2,700 nurses were supported for training, largely in general and child psychiatric nursing. Approximately 2,500 individuals were supported in other program areas: about one-half of these were trained in interdisciplinary pilot projects in such varied areas as law and psychiatry, religion and psychiatry, juvenile delinquency, marriage counseling, teaching emotionally disturbed children, and training for child care workers, community caregivers, psychiatric aides, and others. Thus the 32,925 traineeships were primarily utilized by about 20,500 individuals.

TABLE 3.—*Graduate trainee stipends awarded, and average numbers and amounts of stipends, fiscal years 1962–66*

Fiscal year	Graduate trainee stipends awarded—			
	Number		Amount	
	Total [1]	Average per grant	Total	Average per stipend [2]
1962	4,542	5.1	$17,423,419	$3,836
1963	5,723	5.5	21,774,959	3,804
1964	6,939	5.9	29,038,219	4,185
1965	7,548	5.7	32,510,789	4,307
1966	8,173	5.8	34,724,726	4,249
Total, 1962–66	32,925	5.6	135,472,112	4,115

[1] Excludes undergraduate programs.
[2] Includes tuition and fees in those programs in which funds to cover these costs are usually provided.

It would be worthwhile, in terms of the total program, to review the manner in which training awards have been distributed geographically since the inception of the program. More than one-third of all training funds provided during the period 1948–1965 were awarded to training institutions in the Northeast region of the United States, which includes about one-fourth of the total U.S. population.[21] One-fourth of all awards were to institutions in the North Central States, which include 28 percent of the population. Training institutions in the South, which includes 30 percent of the U.S. population, received 23 percent of the funds awarded. Except for a small amount of support to training institutions in Puerto Rico, the balance of training funds (16 percent) was awarded to institutions in the West. This percentage compares closely with the proportion of population included in the Western region.

The amount of funds awarded has varied widely among the States, largely as a function of the availability of mental health training facilities. Of the total provided from the beginning of the program through 1965, 47 percent has gone to training institutions in New York, Massachusetts, California, Pennsylvania and Illinois.

As would also be expected from the pattern of total program awards, training institutions in the Northeast were awarded the largest numbers of trainee stipends. Awards of stipends in the North Central region and in the West have been in approximate proportion to the population of those regions, while the South has been less adequately represented. The five States of New York, Massachusetts, California, Pennsylvania, and Illinois each received more than 2,500 graduate trainee stipends, providing training for somewhat fewer trainees, since in most instances persons receiving stipends are supported through more than one year of training. These same five States accounted for 46 percent of all graduate trainee stipends awarded during this period.

[21] Data not yet available through Fiscal Year 1966.

TABLE 4.—*Distribution of mental health training funds by geographic region and division, fiscal years 1948–1965*

Geographic region and division	*Percent of funds awarded*
Northeast	35.6
New England	13.0
Middle Atlantic	22.6
North Central	24.8
East North Central	15.0
West North Central	9.8
South	23.1
South Atlantic	13.6
East South Central	3.8
West South Central	5.7
West	15.9
Mountain	3.6
Pacific	12.3
Puerto Rico	.6
Total	100.0

1. Distribution of awards among grantee institutions

The total number of training institutions receiving grant support has also increased, in keeping with the growth in numbers of training projects supported each year. A total of 630 schools and other institutions received NIMH grants for the training of mental health workers in fiscal year 1965.[22] Some 360 institutions received support for training at the graduate level, while 188 (including many of the same institutions) were awarded grants for undergraduate training. In addition, 225 mental hospitals and institutions for the retarded were awarded grants for the training of subprofessional staff, chiefly psychiatric aides, attendants, houseparents, etc. Ten training institutions were each awarded funds amounting to more than $1 million in fiscal year 1965. Funds received by these ten institutions amounted to 18 percent of the total funds awarded for mental health training in that fiscal year.

Of the 630 training institutions receiving grants in fiscal year 1965, 270 received awards of less than $25,000. Awards to these 270 institutions, largely State mental hospitals and institutions for the retarded, amounted to slightly over 6 percent of the total funds awarded.

Schools of medicine received about 34 percent of the total amount of training funds awarded in fiscal year 1965. Colleges of arts and sciences, and schools of social work, each received about 13 percent of the total funds awarded, followed by psychiatric hospitals which received 11 percent. Schools and departments of nursing received slightly less than 10 percent. Combined, these types of training institutions received more than 80 percent of all training funds provided in grants during fiscal year 1965. Major recipients of grant support among other types of organizations were general hospitals, colleges of education, residential treatment centers for the retarded, schools of public health, and various types of mental health clinics. Grants were also made to other schools and organizations of a wide variety of types.

2. Total numbers in training in core mental health professions as related to number supported by NIMH training programs

It is of significance to compare data on numbers of persons trained under the NIMH training grants programs with the total numbers of persons in training in the core mental health professions. It is not possible to provide comparable data for the four professions of nursing, psychiatry, psychology, and social work. It is possible, however, to offer brief comments on this relationship as it pertains to each of the core disciplines.

a. *Nursing.*—Enrollment in graduate programs and the number of nurses moving directly into psychiatric-mental health programs upon completion of under-

[22] Comparable data for the period 1948–1966 are not yet available.

graduate study are increasing. NIMH trainee stipends are for master's degree, post-master's, and doctoral education in psychiatric-mental health nursing, and in the behavioral sciences related to mental health. In 1965, 675 trainee stipends were awarded to graduate trainees in clinical programs in psychiatric-mental health nursing which represents a large proportion of graduate students in this clinical specialty. The pool from which nursing draws graduate students is somewhat limited in terms of the nature of the population (largely women) and motivation toward graduate training. Thus the NIMH undergraduate training program in nursing is an integral part of the total training program in nursing. It is intended to increase the potential manpower pool for graduate training in nursing as well as to assist schools in the integration of psychiatric teaching in the total learning experience of nursing students.

b. *Psychiatry.*—As of September 1, 1965, 5000 psychiatric residencies were offered in the U.S. The NIMH awarded 2,097 stipends for residency training for 42% of the total.

c. *Psychology.*—In psychology, and similarly in social work and nursing, the data cannot be as clearly presented as in psychiatry. The reason is that in each of these three fields the area of interest for NIMH is not all manpower trained within the total profession, as is the case in psychiatry. Nor is it possible to delineate precisely the proportions within the individual professions which are within the specific programmatic NIMH interest. Obviously, within psychology for example, clinical psychology is a subspecialty we are supporting. However, we are also supporting programs in social, experimental, physiological, developmental, and other fields of psychology in which the specific training program is of mental-health relevance. In effect, we are drawing on the potential from the total field of psychology and are attempting to increase the proportion of psychologists working in mental health by supporting new training programs which incorporate mental health relevance within the broader field of psychology.

Within the above frame of reference it is of interest to compare the numbers supported for training by NIMH funds with the total number in graduate training in psychology. Graduate enrollment in psychology at all institutions was 13,733 in academic year 1964–65.[23] NIMH training grants supported training in psychology for an estimated 1,280 persons in that year, or 9 percent of the total graduate enrollment.

d. *Social Work.*—In social work, the situation is similar to that in psychology, in that the NIMH training program is primarily concerned with psychiatric social work, but extends to much of the rest of graduate social work training. This is especially true at present when the graduate social work curriculum has recently undergone a major national revision so that training is generic rather than a set of specialized curricula for different subspecialties.

As of November 1, 1965, NIMH supported about 1,650 social work trainees out of approximately 8,380 graduate students (both master's and post-master's) in social work.[24] This is 20 percent of the total in training.

3. Follow-up information on former trainees

In a recent NIMH study, information on various characteristics was obtained from a sample of persons trained under NIMH stipend support between 1947–1963 in psychiatry, psychology, psychiatric nursing, and social work.[25] The distribution by professional discipline and by sex of this group is given in Table 5. (Note: This sample is not completely representative of total population in these four mental health specialties, since they are personnel trained to the graduate level in their respective disciplines.)

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[23] National Institutes of Health, *Resources Analysis Memo No. 9*, May 1966.

[24] Council on Social Work Education, *Statistics on Social Work Education, Nov. 1, 1965, and Academic Year 1964–1965*. New York: 1966, Table 203, p. 19.

[25] Arnhoff, F. N., and Shriver, Beatrice M. *A Study of the Current Status of Mental Health Personnel Supported under National Institute of Mental Health Training Grants*. Washington, D.C.: DHEW, PHS, NIMH (in press).

TABLE 5.—*Percent distribution of mental health personnel by sex and professional discipline*

Sex	Total	Professional discipline			
		Psychiatry	Psychology	Psychiatric nursing	Social work
Male	54	90	75	4	36
Female	46	10	25	96	64
Total percent	100	100	100	100	100
Number of cases	2,613	796	560	353	904

The type of organization in which this group of persons was employed in their principal paid position reflects the varying nature of these mental health professions (Table 6). For example, the psychiatrists were principally in private practice (48 percent)[26] or working in a hospital or clinic setting (35 percent). However, the psychologists were employed primarily in hospitals, clinics, etc. (41 percent and in colleges or universities (29 percent). The employment setting for those trained in psychiatric nursing was, for the most part, either in the hospital or clinic or in a nursing school. The largest number of social workers (46 percent) were also working in a hospital or clinic while the principal paid position for one-third of this professional group was in a health, education, or welfare agency.

TABLE 6.—*Type of organization of principal employer of mental health personnel, by professional discipline*

[In percent]

Type of organization	Professional discipline			
	Psychiatry	Psychology	Psychiatric nursing	Social work
College or university	(1)	29	2	6
Medical school	12	4	(1)	1
Nursing school		(1)	35	(1)
Public health school	(1)	(1)	1	(1)
Other health professional school	(1)			(1)
Industry or business		2	(1)	
Health, education or welfare agency	1	2	13	33
Courts and correctional institutions	(1)	1		5
Elementary or secondary school systems		4	2	5
Hospitals, clinics, etc	35	41	43	46
Research organization or laboratory	3	11	2	2
Private practice	48	5	1	1
Other	(1)	(1)	1	1
Total percent	100	100	100	100
Total number reporting	793	558	350	900
Number not reporting	3	2	3	4

[1] Less than 0.5 percent.

The individual professions show considerable differences with respect to the time spent in professional activities (Table 7). Thus, while over half the time of the psychiatrists and the social workers was spent in clinical services, one-third of the time of the psychologists and only 17 percent of the nurses' time was spent in that activity. Instead, the nurses spent more of their time teaching, supervising and training others, and in administration. The psychologists devoted considerably more time to research than the other mental heatlh personnel.

[26] Seventeen percent of these private practitioners (or 8 percent of the total group of psychiatrists surveyed) are exclusively self-employed. The remaining 83 percent have secondary affiliations with hospitals and clinics (49 percent); medical schools (17 percent) or other academic institutions (4 percent); health, education, or welfare agencies (4 percent); and smaller percentages with research organizations or laboratories, elementary or secondary school systems, courts and correctional institutions, and industry or business.

TABLE 7.—*Average percent of time spent in professional activities, by professional discipline*

Activity	Professional discipline			
	Psychiatry	Psychology	Psychiatric nursing	Social work
Research	7	25	6	5
Teaching	7	18	25	4
Clinical services	58	33	17	57
Supervising and training others	10	8	23	11
Consultation	8	8	10	10
Administration	9	8	18	11
Formal self-training	1	(*)	(*)	(*)
Other	(*)	(*)	1	1
Total percent	100	100	100	100
Total number reporting	772	557	337	883
Number not reporting	24	3	16	21

*Less than 0.5 percent.

In addition to the above data on mental health personnel trained in these broad areas of psychiatry, psychology, psychiatric nursing, and social work, information was also obtained on persons supported for training in related mental health areas. This graduate-level support was provided for training in public health as it relates to mental health, in mental health research in the biological sciences, and in mental health research in the social sciences.

Training in the area of public health in mental health is directed towards the master's degree in public health and attracts professionals from various disciplines. In this survey, for example, 60 percent of the 115 in this sample were nurses and 23 percent were psychiatrists. Health, education, or welfare agencies were principal employers for 43 percent of the group. Hospitals, clinics, etc., employed 18 percent, nursing schools 17 percent, and schools of public health 8 percent of the group. Public health-mental health personnel devote some portion of their time to a wide range of professional activities. The largest amount of time (29 percent) was spent in administration. The group spent 18 percent of their time in consultation, 16 percent in supervising and training others, 13 percent in teaching, 12 percent in clinical services, and 10 percent in research.

Persons who received research training in the biological sciences as related to mental health (124 persons surveyed) were primarily employed by medical schools (40 percent). Other academic institutions were the principal employers for another 10 percent of the group, while 29 percent were working in research organizations or laboratories. In their professional activities, the group devoted 55 percent of their time to research, 18 percent to teaching, and 10 percent in clinical services.

Somewhat similar findings were obtained for those given research training in the social sciences as related to mental health (82 persons surveyed). With this group, 61 percent were principally employed by colleges or universities, 14 percent by health professional schools, and 13 percent were employed by research organizations or laboratories. Forty-two percent of the time of the group is spent in research and an almost equal percent (40 percent) is devoted to teaching.

An overall picture of the geographic dispersion of these mental health personnel was obtained by combining geographic data on all of the above professional disciplines. California ranks highest for State of current employment with 13 percent of the sample working there. Although every State and the District of Columbia is represented, 43 percent of the entire group are employed in California, New York, Massachusetts, Pennsylvania, and Illinois.

Comparison of the numbers employed in the State with the 1965-estimated State population figures gives a correlation of .86, indicating a fairly close relationship between State population density and dispersion of these mental health professionals. The heaviest concentration of all is in the District of Columbia. Among the States ranking highest in numbers employed, Massachusetts, Colorado, Maryland, Minnesota and California also show the highest relative concentration of personnel. The regional distribution shows relatively less concentration of employment in the Southern States and in the Mountain States than in other regions.

II. PROJECTION OF FUTURE MANPOWER NEEDS

From the previous sections of this report, it can be readily concluded that considerable progress has been achieved in the total mental health manpower field over the past fifteen years. It must be recognized, however, that the starting point for this growth pattern was one of severe manpower shortages, with approximately 12,000 mental health professionals (psychiatry, psychology, social work, and nursing) in 1950.

While many citizens are now benefiting and others will benefit from services provided by these trained professionals, many citizens are yet unable to receive adequate services because the overall need for manpower continues to outstrip the supply and also because the geographic distribution of professionals in relation to population served is in imbalance.

The number of positions available and unfilled in the field gives some further measure of need. Recent figures provided by the American Psychological Association Placement Office shows that in 1963 there were seven positions offered for every three applicants. Since it is known that many vacant positions are not listed on the open market and that some of the applicants seeking a change are currently employed, this ratio must be taken as a gross underestimation. In the classified notices prepared by the American Psychiatric Association for its membership, the median number of positions offered each month is 150 and the ratio of total positions offered to total situations wanted is 23 to 1.

In a study of Veterans Administration hospitals and State hospitals for the mentally ill and mentally retarded about one out of every four budgeted positions for staff psychiatrists are unfilled.[27]

Similarly, one out of five budgeted positions for professional registeerd nurses in State mental hospitals and institutions for the mentally retarded as of late 1963 was unfilled.[28]

A survey made by the Division of Community Health Services, PHS, shows that about 16 percent of budgeted positions for social workers requiring specified education and training as reported by 131 State and local health departments were unfilled in 1961.[29]

The rationale underlying the manpower projections in Table 8 is based primarily on supply which realistically can be completely utilized in view of the above indicators of need. This supply is predicated on the assumption that there will be continuing programmatic support with annual increments in sufficient amounts necessary to maintain, expand, and initiate programs capable of providing the trained manpower needed.

The data presented in Table 8 for each of the individual professions of psychiatry, psychology, social work, and nursing were arrived at by a common procedure, although the details differed for each group. Based upon statistics provided by the various relevant professional societies, as well as the various surveys and studies performed by the NIMH, total national manpower figures were determined. From past growth trends, as well as population and academic projections provided by the Office of Education, National Science Foundation, and the Bureau of the Census, the future anticipated growth was calculated, incorporating the differential attrition rates that pertain to the individual professions.

As previously indicated, the manpower problem is compounded by the uneven distribution of professionals within the country. In 1965, there were approximately 18,750 psychiatrists in the U.S. population of 193,818,000, giving a ratio of 9.6 psychiatrists per 100,000 population. Only ten States and the District of Columbia exceed this overall ratio. If the other 40 States were to be brought up to the average of 9.6 per 100,000 without draining from the ten States and the District of Columbia, an additional 4,223 psychiatrists would *immediately* be required. This, in turn, would then raise the national ratio to 11.8 per 100,000. By this minimal standard, then, nearly one-fourth more psychiatrists than presently exist are needed *at the present time*, and would bring the national total number of psychiatrists to approximately 22,800.

In nursing there is an average of 298 nurses per 100,000 population in the United States. However, the State range within the various States is from 121 to 514.[30]

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[27] *Psychiatric Studies and Projects, No. 10, Salary Ranges for Professional Personnel Employed in State Mental Hospitals and Institutions for the Mentally Retarded, September 1963.* Mental Hospital Service, American Psychiatric Association. Washington, D.C.: 1963.

[28] *Facts About Nursing.* New York: American Nurses Association, 1965, p. 26.

[29] Cited in *Closing the Gap in Social Work Manpower, op. cit., p. 17.*

[30] *Facts About Nursing.* New York: American Nurses Association, 1965, p. 11.

In social work the average for the United States is 65 social workers per 100,000 population but some States have less than 25 per 100,000 and other States have between 75 and 100 per 100,000.[31]

As of the end of 1964, there were 11 psychologists per 100,000 persons with a State range of 2 to 22.5 (excluding the District of Columbia which has an inflated concentration because of psychologists in Federal employment).[32]

TABLE 8.—*Projection of total number and annual increments of psychiatrists,[1] psychologists,[2] social workers,[3] and nurses,[4] 1966–72*

At end of—	Psychiatry	Increment	Psychology	Increment	Social work	Increment	Nursing [5]	Increment	Total
1966	19,523	978	14,403	1,200	12,475	1,201	21,159	819	67,560
1967	20,501	1,026	15,603	1,271	13,676	1,303	21,978	1,030	71,758
1968	21,527	1,077	16,874	1,470	14,979	1,403	23,008	1,238	76,388
1969	22,604	1,131	18,344	1,602	16,382	1,511	24,246	1,444	81,576
1970	23,735	1,187	19,946	1,727	17,893	1,281	25,690	1,647	87,264
1971	24,922	1,247	21,673	1,863	19,174	1,387	27,337	1,850	93,106
1972	26,169	1,309	23,536	2,008	20,561	1,500	29,187	2,051	99,453

[1] With 1 or more years of psychiatric training.
[2] M.A. and Ph. D.'s with mental health relevant training.
[3] M.S. in social work with mental health relevant training.
[4] Some training in psychiatric nursing.
[5] Large increments due to output of nurses receiving short-term psychiatric or inservice training.

III. PROGRAM AREA GOALS AND NEEDS 1968–72

A. Psychiatric Nurse Training

In nursing, current programmatic emphasis is placed on: (1) new training approaches and innovative efforts consistent with community mental health nursing needs of the times; (2) short-term training to increase effectiveness and improve utilization of existing manpower; (3) integrative teaching of mental health and behavioral science content in undergraduate and in graduate programs of nursing other than psychiatric-mental health; (4) research training and experimentation to improve existing nursing programs for preventive care and for the care of the acute and chronically ill; (5) collaborative efforts for delineation of training needs of professional and nonprofessional personnel functioning in community mental health services; (6) programs of research training for nurses; and (7) education for consultation in mental health.

These are considered short-term goals set to meet the long-range goals of increasing the quality and number of training programs and resources to insure manpower adequate for providing comprehensive patient care in present and emerging mental health and related programs.

Training at the graduate level must continue to focus on the preparation of individuals for responsible positions in nursing education in universities and other educational institutions and program facilities in service agencies (community mental health centers, hospitals, and other health centers, etc.), and for the expert clinical nursing care of patients in the numerous segments of patient care, and for research, administration, and consultation.

It is anticipated that annual funds for program expansion for the period 1968–1972 will be required for the addition of four new graduate programs (adult psychiatric-mental health nursing and nursing in child psychiatry) and a minimum of four new programs for training in community mental health and in the special areas, e.g., school nursing, mental health in public health nursing, juvenile delinquency. Expansion of training in 10 continuing programs per year to include some training in community mental health and research and to accommodate additional trainees is anticipated.

It is expected that the total number of trainee stipends will be 2,500 in 1972. The career teacher program would be increased to provide training of a maximum of 20 career teachers per year.

A critical area of need in nursing is that of training in research at the doctoral level. The number of nurses qualified for research to increase the knowledge on which nursing practice and nursing education is based must be increased as ex-

[31] *Closing the Gap in Social Work Manpower, op. cit.*, p. 15.
[32] Data based on membership in American Psychological Association as of December 1964.

peditiously as possible. It is necessary, therefore, to plan expansion over the next four-year period to provide a base for solution of this problem. To prepare approximately 290 nurses at the doctoral level for research in nursing and nursing education will require development and support of two new research training programs per year, plus trainee stipends.

For pilot projects in nursing, support is needed for two to four projects in each of the following areas over the next four years: (1) to develop and evaluate programed instruction, (2) to develop methods for evaluation of psychiatric nursing education at all levels, (3) for evaluation of collaborative research training of mental health personnel including nurses (this might be shared by other disciplines or more appropriately classified in general pilot and special project category of support, (4) for special research training conferences to explore research training needs and resources in psychiatric-mental health nursing, and (5) to explore new approaches and methods of training in administration, consultation, and other elements of community mental health.

Special grants for support of an estimated 10 to 15 continuing or short-term educational programs in psychiatric-mental health nursing, and for educational conferences in this field are needed.

To increase the psychiatric and mental health knowledge and skill of the professional nurse in general practice, support for undergraduate teaching is essential in all collegiate schools. These programs provide the major resource for recruitment to graduate programs. Also, an increasing number of graduates of these programs select psychiatric nursing as a nursing field of practice. It is, therefore, necessary that increasing funds be provided for support of teaching and trainees. Ten new programs would be added each year; the expected increase in trainee stipends 100 per year.

B. Psychiatry

It is already abundantly clear that the demand for psychiatrists is rising more rapidly than the current output can hope to supply. The new comprehensive community mental health centers and the medicare program will place immense demands on the profession.

Trends indicate a need for a total of 380 psychiatry residency training programs and 2,700 residency stipends to be supported by NIMH in 1972.

New requests for NIMH support of residency training programs are anticipated to come primarily from existing State hospital residencies and new residencies in general hospitals and community mental health centers. Other increases in teaching costs and stipends will occur due to the expansion of existing residency programs, particularly in major training centers and in the more recently established residency programs. The rising number of graduates of U.S. medical and osteopathic schools will produec at least an additional 400 students in the graduating class eligible for residency training in 1972 as compared to 1967.

Psychiatry special area programs will be one of the most significant fields of growth in psychiatry training during the period 1968–72. This is the focus around which the enormous needs of the mental health field synchronize with the growth of the psychiatry profession.

Four special area graduate psychiatry programs will have to be expanded significantly in the next five years—community psychiatry, mental retardation, crime and delinquency, and geriatric psychiatry. An increase in requests for such programs has already been documented, and it can be expected that the demands will increase on the dwindling supply of well trained specialists in those fields. Regarding community psychiatry, there is now in development an extensive regional training program geared to training in community psychiatry for teachers in the various regions.

NIMH-supported psychiatric research training programs are currently increasing by about two new programs each year. By 1972 there should be about twenty such programs at major medical centers and perhaps at one or two of the larger comprehensive community mental health centers. It should be noted that the increasing demand for service-oriented personnel may create serious problems in the research area in the not too distant future, if such research training programs are not allowed to expand to accommodate young professionals choosing a career in psychiatric research.

NIMH-supported training programs in basic residency and special training for nonpsychiatric physicians (the general practitioner program) have already fallen far behind the current demand. By 1972, the demand for increased training of nonpsychiatric physicians is expected to increase at an evermore rapid

rate. Almost all institutions that currently have four stipends for the basic residency training programs are requesting six and, although some leveling off of such requests can be expected by 1973, the new comprehensive community mental health centers and the new medical schools will certainly be applying. There will also be an increased pool of manpower to fill these programs among the physicians returning from military service who would not pursue psychiatric careers without these stipends.

Undergraduate programs can be expected to increase significantly in number. As of 1967–68 there will be 14 new medical schools and one new osteopathic school under construction and 7 new medical schools beginning construction. All these schools will be accepting students by 1975. In addition, because of Federal and State funds from other sources, all medical schools in the U.S. will be expanding their classes. Because of this there is already a great demand from many schools to raise the $35,000 direct teaching cost limit as well as the number of $600 student stipends which are now limited to 16. Needless to add, all schools already funded continue to request at least the current maximum allowable funding.

The undergraduate human behavior programs continues to expand at the rate of 10–12 new applications per year and can be expected to do so until all medical and osteopathic schools have such programs. Thus, with approximately 106 schools by 1972, it can be estimated that 50 new applications will be received by that time. In addition the expansion of al other medical schools will increase demands for supplemental funds significantly. This area of increased grant support will be urgently needed if medical school departments of psychiatry are to have a meaningful contribution to make in the initial training period of the future physician.

Pilot projects in psychiatry would reflect chanigng patterns of medical education and changing concepts of mental health theory and practice. Trends in psychiatric teaching at the undergraduate level indicate wider use of electives, greater teaching in coordination with other medical specialties, new applications of audio-visual aids, and new pedagogical and testing techniques. The specific application of program learning or teaching machines to the teaching of psychiatry needs to be tested.

Training innovations are indicated in the medical schools to teach concepts of community mental health, particularly as they relate to the public health aspects, to medical students.

Special internships for those physicians planning a career in psychiatry have been tried and new ones are being considered.

New programs of graduate training in psychiatry will apear as patterns of patient care change.

More psychiatrists need to be knowledgeable in community mental health research, mental health consultation, planning and administration, prevention and epidemiology, the law and medicine, and the economics and political aspects of mental health programs. In general, psychiatry as a profession, and psychiatrists as individuals, have done much to change old or inadequate methods of dealing with mental illness, devise new concepts and plans, and lead the implementation of such plans. However, such new programs often require people with new knowledge and skills.

C. Social Work

In social work, the growing interest in the community mental health thrust, has resulted in a perceptible shift toward stressing "sociogenic" and environmental factors as contrasted with essentially psychogenic factors in mental illness. Recent expansion of support will produce personnel for group services, community organization and planning, administration, and research. Training capabilities of training centers in these areas have already begun to respond to pressures from such sectors as the antipoverty program, the expansion of health and medical care services, and the movement in community mental health.

During the period 1968–72, the need to support programs in new schools of social work and new projects in the present group of schools will require forty new projects and 350 stipends a year. These projects should be distributed as follows: five grants in psychiatric social work, ten grants in mental health-related areas, five doctoral, ten pilot, special and undergraduate, and ten projects for career teachers and for senior stipends. During this period it is anticipated that at least five new doctoral programs will be initiated in social work education. Provision should be made in budget allocations for support for new doctoral programs and expansion of support in existing programs to account for anticipated increased enrollments in this segment of social work education which tends to be the leading source for teachers and research personnel in the field.

It should be noted that the number of social workers trained in importantly related areas will also need to be increased. These include social workers in group services, community organization, family and child welfare, corrections and delinquency, narcotic and drug abuse, aging, and alcoholism. There are urgent pressures for social work personnel from newly defined areas of responsibility stimulated by such national programs as Economic Opportunity, Peace Corps, VISTA, and Medicare, involving recently identified tasks associated with mental health-related services in employment centers, race relations, urban renewal, family planning, socio-legal aid, neighborhood-based services, and social intervention in the life of the subcommunity or catchment area served by the new community mental health center.

In the years 1968–1972 the mental health training program will be called upon to move into the area of support for undergraduate education in social work. There are currently one hundred and forty programs represented in the Council on Social Work Education, which will receive a project grant to enable expansion of consultation to these programs. These programs are a means of recruiting to the mental health professions and to positions in the mental health field not requiring full professional training. Mental health funds will be required to improve and extend existing programs in undergraduate education and to develop new programs where these do not now exist. For the time being, stipend funds are not envisioned in the undergraduate area.

D. Behavioral Sciences Training

In behavioral sciences training, future plans in each of the major areas are as follows:

1. Biological sciences

From its inception in 1957, the biological sciences research training program has been one with a special point of view. This support program is concerned with those aspects of the biological sciences and the biomedical sciences that emphasize the concept of behavior; thus, consideration is given to the theoretical and empirical understanding of biological processes that contribute to the understanding of behavior parameters and vice versa. Administratively, the effort has been to develop programs of a multi-disciplinary character that are integrated in their research efforts and are not merely parallel programs. Support is provided for 26 research training programs providing stipends for 256 trainees (121 predoctoral and 135 postdoctoral).

Since 1962, three phases in the development of the support program have become evident: (1) the psychopharmacology research training programs involving departments of pharmacology with support or cooperation of departments of psychology and psychiatry, (2) on-campus research training programs involving zoology and/or biology departments with strong offerings in experimental psychology, and (3) research training in medical centers and affiliated institutions in the brain-behavior sciences.

In addition to the continued development of areas of brain behavior and psychopharmacology, new programming will emphasize the field of neurobiology. The elements of this field, which include behavior genetics and the psychobiology of adaptation and development are considered to hold unusual promise for basic research on mental problems and are clearly in need of increasing numbers of well-trained investigators.

From the current base of 26 programs involving support for 256 trainees, it is anticipated that 6–9 new programs per year involving approximately 75 additional stipends will be ready for support. By 1972 the biological sciences research training program should reach a level of 60–65 programs supporting approximately 650–700 trainees.

2. Psychology

Program support projections for psychology can be understood only in relation to the pattern of support over the past two decades and the potential that support has helped to create. From 1947 to 1957, this program focused on the production of professionally trained manpower in psychology and indirectly on the development and elaboration of the scientist-professional model for training and functioning in the area of clinical psychology. In the second decade of support, 1957–1967, the growing and related needs for research psychologists (as producers of new knowledge and as teaching personnel for research and scientist-professional programs) led to an emphasis on substantive and methodological research training projects. These projects included the areas of learning, perception, physiological psychology, personality, motivation, social

psychology, developmental psychology and a few specialized areas such as measurement and psycholinguistics. At the same time, support for scientist-professional training was continued and a pattern of experimental support for other scientist-professional areas and other models of training was added.

The following program growth appears to be feasible over the next five years. The emphasis on training of research psychologists should be increased (1) to permit a broad research capability for developing new knowledge in the basic parameters of human experience and behavior, and (2) to provide manpower with research and evaluation skills that will be needed in the assessment and modification of the developing programs involved directly in societal problems. In addition, the broadening of this research training base provides the means whereby additional applied or more specialized programs in psychology may be readily developed. Currently, there are approximately 130 institutions which grant a Ph. D. in psychology, although only 42 of these now receive support for 56 training projects. Estimates are that by 1975 there will be over 200 Ph. D. granting institutions, each of which would be able to utilize a minimum of one research training project for development and expansion. The needs of the field and these training institutions can absorb an additional number of programs averaging about 20 a year during the next five-year period.

In the special and experimental areas that have been supported, there is also the potential for a significant expansion at this time. These areas include school psychology, community psychology, and centers for the integration of research, training, and professional engagement. Specifically, emphasis should be placed on the preparation of psychologists trained to function in school settings in a variety of capacities, and on the development of training capabilities in the community and socially oriented approaches of psychology. At least 16 programs in these areas can be developed each year during the next five years. As psychologists have evolved a science-profession orientation and have assumed broad responsibilities for developing behavioral science knowledge as well as translating it into meaningful articulation with society, an increasing variety of programs have developed in the discipline. An important concomitant of the growing complexity of the area is the need for training research, and service centers which function as training laboratories. Such programs can be expected to include basic research investigators, traditional university training programs, and innovative societal engagement programs. These centers will not only study and implement new approaches to the involvement with societal problems but also will provide a training milieu for students. It is estimated that each year, for the next five years, two major centers can be developed.

Clinical psychology support is provided for almost all existing approved university programs. Nevertheless, there are important needs to broaden the base of this training particularly in regions of the country with shortages of scientific and professional manpower. Increasing the emphasis on providing support for the development of clinical psychology programs rather than merely adding to the support of existing programs would significantly add to the numbers of professional manpower and to the base for producing such manpower in future years. These developments, plus badly needed expansion of child clinical training, and a modest increase of postdoctoral training in university settings can be implemented with the addition of approximately 20 more programs a year.

Given such a pattern of support, the Institute can provide the necessary leadership to support psychology training in many universities to the extent that 300–400 additional Ph. D.'s might be added to the total of 1,200 now annually receiving the degree in psychology.

During fiscal year 1967, funds have been provided for 239 programs including 1,652 stipends. The estimate of potential growth listed above would add annually approximately 58 programs and would include 350 additional stipends.

3. Social sciences

This program was begun in 1957 as part of the broadened support approach of the mental health institute. Initially the program was limited to portions of social sciences areas with visible reference to pressing mental health problems. Thus training programs in social science focussed on circumscribed aspects of the sociology of medicine in mental health, community mental health, social psychology, and social disorganization and social problems. In the recent past, an effort has been made to broaden the scope of training projects to include the family, culture change, linguistics, and ecology as well as an emphasis on research methodology.

The training support program in social sciences, which started with two projects in 1957, currently supports 65 programs and provides stipends for 468 students.

The new support areas are being developed in political science and economics which can contribute toward meeting the urgent need for persons in decision-making areas (i.e., psychiatrists, lawyers, city planners, public servants) to be highly informed about those areas of political planning and administration which relate to planning and implementation of mental health activities. Persons at the service frontiers also increasingly require information on the political and economic realities which underlie all mental health and social problem endeavors.

The continued development of these programs will seek to supply additional well-trained investigators studying human behavior in the social context. The research areas involved include the social determinants of mental illness, and the conceptualization of positive mental health models to be understood in the sense of productivity and creativity as well as by means of those influences leading to conformity and adjustment. Increasing emphasis needs to be placed on understanding of family and social therapies and there is an immediate need in the new community mental health centers for the development of a more sophisticated ecology.

The development of programs in economics, political science, urban studies and other areas that can be expected to make a major impact on the parameters of mental health has just begun. It is estimated that there will be approximately six programs in these areas available for support during each of the next five years. By 1972, it is anticipated that the program could include 30 programs supporting approximately 350 students in these areas.

It is anticipated that the social sciences program growth should reach approximately 100 grant programs supporting 1300 students within five years.

4. Research fellowships program

The research fellowships program is training behavioral scientists who have a high potential and a firm career interest in research. Research fellowships are awarded to behavioral scientists at all levels, beginning with predoctoral fellowships for the most promising of the graduate students. Postdoctoral research fellowships provide for immediate advancement in behavioral theory and research for recent Ph. D.'s and M.D.'s. Special research fellowships enable the experienced research scientist and clinician to use a year or two of time to be devoted entirely to advanced studies which will strengthen or enlarge his research skills, or enable him to broaden his perspective through intensive examination of the theoretical bases for research in his field or through interdisciplinary, comparative, or cross-cultural studies.

The strength of the research fellowships program lies not only in the production of highly qualified research scientists but also in its flexibility. The individual applicant may select the sponsoring institution which he believes is best equipped to provide a research training program to fit his own objectives as a behavioral scientist. The sponsoring institution, in turn, expresses its desire to work with the individual applicant and pledges itself to provide the professional guidance and the facilities which will best enable the individual to develop his potential. The program is available to applicants from large and small institutions alike. At the postdoctoral and special levels, approximately five percent of NIMH fellows study overseas each year. Fellowships may be awarded for advanced work with outstanding scientists in other countries—with the result that the best opportunities on a worldwide basis are open to NIMH fellows who seek to supplement their work in the United States by becoming directly involved with the often unique work of foreign scientists.

The fellowships program is essential in achieving the overall objectives to develop scientific research and professional manpower in all of the mental health fields. Fellowship awards lend balance to the training programs and broaden the base of support by making a wider variety of types of training available to many individuals whose needs may not be met by the institutional grants. Specifically, the fellowships program: (1) coordinates fellowships with training stipends that are awarded by institutional projects so as to allow for the development of the particular research specialization of individuals that may not be covered in the more broadly based training programs; (2) provides for the development of research training in projects and areas that are not yet sufficiently developed to merit full-scale training program support.

This program also aids in the development of the research capacity of individuals in mental health areas such as psychiatry and social work that are not specifically focused on research during the basic preparation of the student.

Academic Disciplines of Fellows: Two-thirds or more of the NIMH fellows are working in psychology, psychiatry and related medical sciences, and in pharmacology. While these disciplines are commonly recognized for their concentration on problems related to individual behavior and mental health, relevant research contributions are also coming increasingly from other social and biological sciences.

Research Areas and Fields: Specialists working in many different research areas are making contributions which are advancing knowledge related to mental health and mental illness. Table 9 is a condensation of a detailed analysis which was prepared to show the research areas represented in the fellowship programs of fellows whose awards were made from fiscal year 1965 funds. Over the years a good balance of support over the four major categories (I–IV) has been maintained. It is hoped that support in area II, the direct study of mental development and mental illness, can be stimulated and increased in the near future, particularly through the attraction of psychiatrists and clinical psychologists at postdoctoral and special levels. Direct attacks on mental health problems are also made by investigators in the other three principal areas. Brain studies, biochemical and drug studies, and the study of genetic determinants are recognized, for example, as being especially promising for acquiring new knowledge which may be applied in the treatment of the mentally ill. It is estimated that at least 35 percent of the research efforts in the fellowships program are of the type which will be immediately and directly applicable to mental illness, although the 155 fellowships listed under area II represent just 18 percent of the total number of fellows supported from fiscal year 1965 funds. The other 65 percent of the fellows have research interests in areas essential to the understanding of the physiological, psychological, social, and cultural factors pertinent to the maintenance of mental health or contributing to the incidence of mental disturbance or illness.

Projection of Program Needs: During the decade of the 1960's it has been the hope and the objective of NIMH that the research fellowship could be used with increasing effectiveness for the recruitment of behavioral scientists and for training in research relevant to mental health, and that over the whole period it will make a significant contribution toward producing the manpower needed in research. In recent years the succes of the program has been limited by financial inability to award fellowships to all of the promising applicants proposing study and research programs recommended for approval by the reviewing committees. In fiscal year 1966 only about 45 percent of applications recommended for approval could be paid.

The projection of program needs through fiscal year 1972 is based on two objectives: (1) to utilize more fully the untapped manpower and training resources now available for behavioral research, and (2) to encourage the development in the community mental health centers of a research focus and of opportunities for research training. The new community centers will constitute on-the-spot training opportunities, where research efforts can be integrated int othe total mental health program. A number of the universities are planning to work closely with the centers, utilizing the centers as their own bases for training for clinical research and clinical service. The research fellowships program, with its flexibility for tapping all appropriate sources of research training, will be indispensable to many of the universities and centers in making it possible for them to carry out their own aims for participating in the advancement, through research, of knowledge basic to clinical and preventive practice. The fact that new approaches to treatment and to the prevention of mental illness are needed to meet community-wide needs, will broaden research on the social factors relevant to mental health as well as on research on clinical methods.

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TABLE 9.—*Number of NIMH research fellows in each research area, fiscal year 1965*

Research area	Total	Predoctoral	Postdoctoral	Special
I. Biological and physiological correlates of behavior	(184)			
Brain studies	80	51	22	7
Biochemical studies	21	15	4	2
Mechanisms of drug action	21	14	4	3
Sex, reproduction, and genetics	20	18		2
Sensory processes	17	14	2	1
Other (autonomic nervous system; digestion and nutrition; heart and circulatory system; motor functions; respiration; sleep, rest, fatigue; etc.)	25	15	6	4
II. Psychiatric and psychological study of mental development and mental illness	(155)			
A. Disorders (etiology, diagnosis, and psychopathology):				
Personality structure and dynamics	44	39	1	4
Psychosocial developmental studies	26	18	6	2
Schizophrenia	19	15		4
Delinquency and criminality	14	6	1	7
Mental retardation	13	13		
Other (alcoholism, drug addiction, brain damage, child behavior disorders, psychosomatic disorders, sensory and functional disorders, etc.)	21	16		5
B. Treatment of disorders	18	14	3	1
III. Psychosocial and cultural correlates of behavior	(274)			
Community structure and dynamics, social change	79	72	2	5
Behavior of groups	54	49	2	3
Language and communication	23	15	3	5
Family structure and dynamics, marriage, and divorce	21	16	1	4
Educational processes and socialization of child	21	16	4	1
Animal studies of social interaction	21	13	8	
Attitudes, values, and interests	20	20		
Social factors in treating mental illness	15	6		9
Social perception and cognition	14	13		1
Other	6	5		1
IV. Basic psychological processes	(232)			
Learning	102	84	16	2
Perception and psychophysics	46	41	3	2
Cognitive processes	30	25	1	4
Psychometrics, statistical design, and computers	20	12	5	3
Motivation	11	11		
Theory and methodology	6	3	1	2
Emotional processes and stress	5	4	1	
Other	12	8	2	2
Total, all research areas	845	661	98	86

NOTE.—Each fellow counted only once in primary area of research.

In fiscal year 1967, the NIMH program will support approximately 895 research fellows, at all levels of awards, with a total budget of $5,343,000. It is estimated that in response to the demands made upon the program, including the requirements for the newer approaches to the control and prevention of mental illness, 400 to 500 awards should be made in each of the subsequent five years, so that in fiscal year 1972, 3200 fellowships would be provided in all areas and at all levels.

5. Research career program

To provide an investigator with freedom to devote himself full time to research and related activities, to give him the opportunity for maximum productivity, and to assure an acceptable continuity of support is the function of a research career program award.

The immediate goal of the research career program in the field of mental health is to continue and increase the salary support of investigators who have demonstrated their capacity to produce effective research. It is important to recognize that such awards will be made, in the future as in the past, only for scientists who need salary support to have the major part of their time made available for the pursuit of research.

Currently, the program supports 139 research scientists who have positions in 69 institutions throughout the United States. During the current year, it is probable that this number of scientists will be increased by 25. The importance of the group to mental health research is to be understood not only in terms of their independent contributions by experimental projects and theoretical advance-

ment, but also because they constitute an extremely effective corps of research teachers throughout the spectrum of sciences relevant to mental health problems.

The majority of the scientists in the research career program are supported either by research career awards, indefinitely renewable, which were closed to new applications in fiscal year 1964, or by research career development awards, at the group 2 level. The group 2 award is restricted to scientists who have demonstrated their promise by experimental work, but whose potential for original contributions, either with respect to the substance of their projects or the theoretical objectives, may be realized only through continued research experience.

Of the 208 awards which have been made in the NIMH research career program, 52, or 25 percent, have been made at the level of the career development, group 1, award, which is designed primarily for the recruitment of promising young scientists to mental health research. This award provides an opportunity for a young scientist to devote himself on a full-time basis, and for a period of five years, to research activities, including such additional training as will qualify him for fully independent research work. This unique feature of the NIMH research career program is a continuation of the former mental health career investigator grant, which became available in fiscal year 1954, and is designed mainly to strengthen research on problems of clinical psychiatry. Applications have been especially invited from young psychiatrists, and the hope has been that a sufficient number of research psychiatrists would be trained to relieve a generally impoverished situation with respect to research staff and research programs in the psychiatric departments of American medical schools and other appropriate institutions.

Since evidence of the results has accumulated during a period of twelve years, there is a solid reason for the belief shared by all who have had to do with this type of award that it serves an unusually important function. Former "career investigators" are recognized throughout the United States as leaders in psychiatric research. The present group supported by group 1 awards, numbering 37, is contributing productively both to the research projects and to the development of plans for research and research training among 23 of the Nation's psychiatric centers. Of the 41 psychiatrists who have completed their tenures of support in this segment of the NIMH program, represented by the former career investigator grant as well as by the current group 1 award, 28 have continued in full-time research positions and 9 are continuing in academic psychiatry with approximately an even balance between experimental work and clinical, teaching, or administrative activities. The number who have definitely turned away from the research career is 4, or 11 percent. Vigorous cultivation of the career development, group 1, award is an immediate goal for research on problems of clinical psychiatry.

Achievements of the NIMH research career program may be described in terms of the continuity in research and the productivity of the scientists who have been supported. The breadth of the program is also significant, in terms of the disciplines represented by the investigators, the kinds of institutions where they are employed, and the number and distribution of these institutions. The breadth and vitality of the NIMH research career program is demonstrated by Table 10 which shows the disciplines of the investigators, classified by levels of support.

TABLE 10.—*Disciplines of investigators supported to date by the career investigator grant and research career programs of the National Institute of Mental Health*

Disciplines	Number of investigators supported by each type of award			
	CIG and Dev. group 1	Dev. group 2	Career award	Totals
Medical:				
Psychiatry	55	17	4	76
Pediatrics	1	1		2
Internal medicine	1	1	1	3
Internal medicine-biochemistry		1		1
Neurology	1		2	3
Epidemiology		1		1
Pharmacology			1	1
All medical	58	21	8	87
Other biological:				
Biochemistry	1	4		5
Zoology		2		2
Neuroanatomy			1	1
Audiology	1			1
Physiology		1		1
All biological	2	7	1	10
Behavioral science:				
Psychology	11	53	18	82
Sociology	1	6	1	8
Anthropology		4	2	6
All behavioral	12	63	21	96
Total	72	91	30	193

Mental health investigators supported by the research career program are engaged in the study of a broad range of problems, both clinical and basic, for which it is essential that additional knowledge be produced in order to improve the effectiveness of the contribution of the behavioral sciences to mental health. A brief description of the work now being accomplished by these investigators will identify the nature of the contributions which may be expected.

About 30 percent of the scientists supported by the research career program are working on research directly relevant to clinical problems, including studies on schizophrenia, depressions, neuroses, psychosomatic disorders, alcoholism, mental retardation, the use of psychopharmacological agents and the effectiveness of psychotherapy.

Approximately 30 percent of the investigators are engaged in basic studies of biological and physiological processes fundamental to the understanding of behavior. They study problems in neurophysiology, neurochemistry, and basic biochemistry, in the function of the autonomic nervous system, in endocrinology, neuropharmacology and genetics. Others in this group are investigating the mechanisms of sleep and fatigue, metabolic functions of importance in the control of behavior, and factors in growth and development.

A third group, about 25 percent of the investigators presently supported, is attempting to increase our understanding of psychological capacities and processes, such as learning and motivation, perceptual and cognitive functions, intelligence, emotional processes, personality structure and dynamics, language and communication.

The remaining group, about 15 percent, is engaged in research on social processes and sociopsychological correlates of behavior. Among the areas of special interest are aspects of child development, family structure, small group behavior, factors in community structure and dynamics, and the nature and development of human attitudes and values.

If the kind of research which has been encouraged by the NIMH research career program is to be continued and further developed, it will be necessary to maintain salary support for most of the investigators with career development awards (group 1 and group 2), and also to attract other scientists with an outstanding potential to the pursuit of research in appropriate settings. Other

sources of funds are still quite inadequate to maintain the investigators currently employed, not to mention the need for additional research scientists in the mental health centers—notably the departments of psychiatry in medical schools, the psychiatric and general hospitals, the institutes of the behavioral sciences, and the nonaffiliated biomedical research institutes.

It is proposed, therefore, that the current program of salary support for mental health investigators be continued and expanded, with no diminution of effort to nurture the research which is presently being accomplished.

In fiscal year 1968 it is estimated that the total number of awards should be approximately 190 (including about 140 committee continuations). In each of the subsequent years it is estimated that 12 to 15 young investigators of promise may be recruited to begin careers of research in mental health with the support of career development, group 1, awards and that 20 to 25 investigators fully qualified for independent research will be recommended for career development, group 2, awards. Maintaining salary support for most of the investigators now in the NIMH research career program, and expanding the program by 32 to 40 new awards each year will require an annual increase of funds after fiscal year 1968 averaging approximately $950,000, reaching a total expenditure in fiscal year 1972 of approximately $8,000,000 for approximately 335 awards.

6. Special programs

The organization of the Behavioral Sciences Training Program represents, in part, the response of the Institute to the increasing use of the term "behavioral sciences" in the field and, more importantly, the recognition of commonalities among various disciplines and scientific areas. While there is no generally agreed upon definition as to what comprises behavioral science, it is true that the evolution of certain biological science areas, psychology and the social sciences has reached a point where the overlap and interdependence among these areas is visible. The Special Programs Section has been organized in an effort to increase the probability that the collaborative efforts among these scientific areas be provided with such appropriate training support as is necessary for their development.

In pursuing the goal of providing support for the training and advanced education of broadly based behavioral scientists and professionals, efforts have focused on the academic and research institutions of the Nation and the philosophy of the support program has been largely continuous with the existing academic purposes of research and teaching. However, the general academic purpose is changing and expanding. In part, these changes reflect the increasing recognition of the substantive interdependence of various scientific domains such as behavioral sciences and are concretely illustrated by the rapid development of centers and institutes within universities to allow the interchange of ideas and the conduct of multidisciplinary research.

To some extent, collaborative training efforts are currently being supported within the Biological Sciences Program. However, this program emphasizes training in those areas where biological constructs and the behavioral dimension come together. The potentials of training within multidisciplinary programs involving the psychological and social sciences have as yet not been realized. It would be the function of the Special Programs Section to encourage and foster the appropriate development of such programs so as to permit a broader investigative contribution of the behavioral sciences to all aspects of mental health.

E. Experimental and Special Training Program

1. Program objectives

The general mission of the Experimental and Special Training Program is to plan, administer, direct, and coordinate a national program of training grants for (1) new, unique, innovative, and exploratory time-limited mental health training projects directed to personnel allied to the mental health effort and the training of inter-disciplinary groups of mental health workers; (2) programs in special areas such as community mental health, narcotic and drug abuse, alcoholism, suicide prevention, crime and delinquency, childhood mental health, and recruitment; (3) the extended support and replication of meritorious pilot and other training projects; (4) the mental health-public health training of students enrolled in the Schools of Public Health in the United States; and (5) the convening of training workshops, conferences, institutes, and surveys concerned with curriculum development, dissemination of training information, and training in special areas.

The training emphasis may be on the development of programs for mental health related personnel, research training, continuation or extension of training, training new types of mental health personnel, training techniques and methods, or preservice training.

A key factor in the Experimental and Special Training Program is the requirement that grantees evolve a model for training which they have tested out and evaluated. These models are then made known to other training institutions which might wish to adapt or adopt features of the grant program. Efforts are made to provide grant support where major diffusion of findings will result, and where grant support can provide a crucial point of intervention within an area of training, a profession, or a social system.

Support is also available to Schools of Public Health for the expansion and improvement of the mental health content of the curriculum both for the general student body and for specialty training in public health-mental health.

Special Grants are provided for various training activities such as conferences, institutes, workshops, and demonstrations.

2. *Contemplated activities, trends, and needs*

a. *Training for comprehensive community mental health centers.*—It is anticipated that the development of comprehensive community mental health centers will be accompanied by demands for new and different types of personnel to staff these institutions. Models must be formulated and tested in order to create, on a broad scale, the necessary personnel, many of whom will be of a subprofessional character. One of the missions of this program is to promote the development and testing of these models, so that knowledge may be gained about the jobs to be performed in the various services which comprise the comprehensive community mental health center. Several models have evolved for training personnel to staff inpatient, outpatient, consultation, and rehabilitation services, as well as for the training, research and evaluation, and administrative functions of centers.

b. *Increased demands for training in "pressure areas."*—As programs in the so-called "pressure areas" of delinquency, narcotic and drug abuse, mental health administration, mental health communication, and community mental health are expanded within the NIMH, there will be need to meet the challenge of opening up training opportunities for personnel to work in these fields.

c. *Increase in numbers and types of personnel to be trained.*—The need to provide appropriate training models for the many kinds of persons having community mental health-related job responsibilities will continue to be acute. Likewise, mental health manpower, in all job categories, will be needed increasingly. Mental health training has progressed past mere desirability to a necessity for maximal functioning among such groups as school teachers, clergymen, lawyers, school administrators, correctional workers, judges, police, and welfare workers, to name just a few community agents. Under the Experimental and Special Training Program, numerous types of community agents are being trained for active participation in mental health work.

d. *Increased demand for training in new and special areas.*—Music therapists, occupational therapists, journalists, and recreation workers illustrate just a few of the groups which are seeking mental health training and for whom initial support via a pilot project has been provided. The mission of this program calls for developing programs in the following areas which have not received support: indigenous, subprofessional community personnel; geriatrics workers; city planners; and art therapists. In addition, it is recognized that while new areas are being explored and tested, demands will continue for the increase in training opportunities for such groups as the clergy, school personnel, and research workers.

e. *Broadening of the types of training settings.*—Increasingly, public, private, and nonacademic research and service agencies or organizations are seeking to utilize their facilities and staffs, independently and/or cooperatively for mental health training, both preservice and inservice. This development would appear to be a function of the growing emphasis upon the intern, journeyman, or apprentice training model as well as the increase in applied research concerns, and new patterns of care.

The proliferation of qualified training centers has increased significantly the potential number of applicants who are ready and able to undertake new, innovative patterns of training aimed specifically at the wide variety of ancillary personnel within a community who can contribute meaningfully to mental health efforts.

f. *Need for a multipurpose mental health worker.*—As efforts continue to develop sufficient manpower to serve specific specialized mental health functions, there appears to be need to create a multipurpose mental health worker who would be a generalist. Such a worker would have multiple skills including those needed for consultation, community organization, training, research, clinical work, and administration, or some reasonable combination of these areas.

F. Continuing Education Program

1. Program objectives and priorities

The broad objectives of the program in Continuing Education are as follows: (1) to increase the effectiveness of existing mental health manpower of all types wherever they may work; to make continuing education and staff development a built-in component of service, training and research programs in all mental health settings; (2) to meet the immediate and urgent need for successful implementation of the Community Mental Health Centers program so far as effective utilization of manpower is concerned; (3) to foster the development of continuing education as a type of education, i.e., make it a much stronger component of the mental health educational programs within universities and training centers; and (4) research in continuing professional development, learning styles and work-learning processes; evaluation of continuing education programs and methods. Initially, priority will be given to projects with one or more of the following emphases: (1) development of strong continuing education divisions within training centers for the mental health professions, increasing the amount and quality of continuing education resources available in the vicinity; (2) continuing education which is an integral component in the implementation of community and State mental health planning efforts; (3) projects with a program development emphasis, targeted to the needs of a specific group of potential trainees, as compared to offering isolated courses to whoever may be recruited; and (4) research and evaluation projects, preferably built into active continuing education and staff development programs.

2. Potential training centers

There are currently approximately 95 medical schools, 287 psychiatry training programs, 65 schools of social work, 140 major departments of psychology, 880 diploma, 188 baccalaureate, 53 masters, and 3 doctoral programs in nursing in the U.S. which are potentially eligible for grants to develop continuing education programs. It is anticipated that there will be considerable growth in the number and size of these programs in the next 5 years. In addition, there are a large number of other graduate and undergraduate training programs, including social sciences, biological sciences, public health, education, law and theology which may be eligible for support or collaboration in continuing education relevant to mental health. For example, there are approximately 125 undergraduate departments of colleges and universities offering courses with social welfare content. Possible grantees also include regional agencies, the 53 States and Territories, numerous mental health clinics and hospitals, professional societies and associations, as well as a variety of public and private social and health agencies. Special regional centers for continuing education may also need to be established.

Sound program development will also require support of research and evaluation projects plus application of new technology. These should include: basic research in professional development, patterns of practice, work habits, learning processes, etc.; evaluation of individual continuing education projects and teaching-learning methods; experimentation with newer continuing education methods and communications technology; more specific analysis of the needs of the field; and collaborative research projects involving several continuing education centers. Potential grantees may include any of the previously mentioned institutions and agencies, and contracts may be developed with industry and special educational foundations or institutes.

3. Program areas

a. *Professional training centers.*—It is estimated that during the fiscal year 1968, approximately 80 professional training programs in psychiatry, psychology, social work, nursing and social sciences, will be funded to enable them to establish or expand their continuing education programs. Based upon the funds needed to provide minimum basic support of such programs, approximately $40,000 per institution, or $3,200,000 would be required.

b. *G.P. postgraduate education.*—The NIMH support of postgraduate training programs for nonpsychiatric physicians has lagged far behind the current demand. In the interest of providing the best medical and mental health care, continuing education in psychiatry should be made available to all practicing physicians. To achieve the ultimate objective of providing appropriate psychiatric training for every physician, and to help meet the program needs and objectives of community mental health centers, many of which will be based in psychiatric units of general hospitals, a significant expansion in grant support is essential.

In addition to the establishment and support of continuing education divisions in departments of psychiatry, it is proposed that there should be a G.P. postgraduate education programs centered in the 178 metropolitan areas of 100,000 or more population. Some of these grants will be made with national medical organizations for purposes of fostering program organization and development. It is estimated that during fiscal year 1968 it will be possible to fund 15 new projects for a total of $250,000.

c. *Other training programs and resources.*—In order to stimulate and involve State mental health agencies, regional organizations and national professional associations and agencies, in the development and expansion of their continuing education activities related to mental health, it is estimated that during fiscal year 1968, it will be possible to fund at least 20 programs at $30,000 each for a total of $600,000. It is anticipated that such training programs would provide direct training experiences such as institutes and seminars for employees, coordinate training efforts in the various institutions and agencies where appropriate, develop meaningful linkages with institutions of higher education in the State and regions, and provide a vehicle for the development of training aids and materials.

Regional bodies, responsible for training functions within specified areas of the country, will need to develop and carry out programs designed to meet regional needs. In addition, national professional organizations and agencies have expressed a desire to develop a variety of training approaches to meet the needs of target groups such as psychiatrists, social workers, etc.

It is also estimated that $250,000 will be awarded to fund a minimum of 10 programs of continuing education in public and private service agencies (hospitals, clinics, mental health centers, family and children's agencies, etc.) during the fiscal year.

d. *Conferences.*—During the fiscal year 1968, it is planned to hold 5 regional conferences for college and university faculty and service agency personnel involved in continuing education, at a cost of $30,000 each for a total of $150,000. Since the ultimate success of a continuing education program hinges so directly upon the close collaboration of institutions of higher education and individuals and agencies providing direct mental health services to people, it is essential that adequate provisions and opportunities are made for an appropriate exchange among them. The five conferences proposed would be aimed at this objective. They would be held in strategic locations in the U.S. and would involve individuals in leadership positions. Each conference would have from 75–100 participants. It is expected that these conferences, which would be multidisciplinary in nature, would determine and help initiate a general plan and approach for more effective programming and implementation of continuing education activities designed to meet the needs of mental health personnel.

IV. BUDGET NEEDS TO MEET THE MANPOWER GOALS: 1968–72

A. Training Programs

In the original long-range projections made in 1963 when the community mental health center legislation was passed, the entire mental health program budget was developed through 1973. As one part of that long-range budget plan, estimates were made as to funds needed in training programs to meet the manpower requirements for the total mental health program from 1963 through 1973. Those estimates indicated annual increases averaging approximately $15 million per year. Thus, the funds for training were to increase from a level of $50 million in 1963 to $185 million in 1972. In actual fact, with the exception of the allocation for 1964, the increases to-date have not averaged the projected levels. In 1967, the appropriation indicates a level of $94,448,000 for training. Since the original projections called for almost $114 million this means that in the four years since the initial estimates, the actual level has fallen almost $20 million below the projections. The full impact of this difference has not yet been felt, since the graduates of these programs do not get into the manpower pool until three to four years after they commence graduate training.

In order to return the rate of growth to the original projections, levels of annual budget support for the training program have been developed, beginning with the 1968 allocation and extending through 1972, as shown in Table 11. It will be noted that the most rapid rates of increase are in the continuing education and the experimental and special training programs. Research training and undergraduate programs are the next in order of relative emphasis. The importance of these areas of training has already been emphasized in the previous narrative. At the same time, substantial annual increases are needed in the basic graduate training programs to obtain the bulk of the needed manpower.

A special allocation is made for funds to provide for dependency allowances for persons receiving trainee stipends. The mental health training program is the only NIH program which does not provide such dependency allowances. The continuing effort to make stipends in all PHS training programs reasonably comparable necessitates such an adjustment in the mental health program.

Because of the size of the program, such an adjustment cannot be absorbed within the regular increases. It is estimated that the overall average number of dependents is slightly less than one. Translated into dollars and based on the usual $500 per dependent, it would require an average of about $400 for each of the estimated 10,000 trainees in 1968. The total funds required would be $4,000,000 in 1968.

TABLE 11.—*Training program budget needs, 1968–72*

[In thousands]

Major program areas	1967 allocation	Projected needs				
		1968	1969	1970	1971	1972
Undergraduate	$8,500	$9,500	$11,000	$12,500	$13,500	$14,500
Graduate	76,148	90,000	104,000	118,000	131,500	145,000
Research	(10,500)	(12,500)	(14,000)	(15,500)	(17,000)	(18,500)
General practitioner	(10,000)	(10,500)	(11,000)	(11,500)	(12,000)	(12,400)
Psychiatry, psychology, social work, and nursing	(49,848)	(59,000)	(69,000)	(79,000)	(89,000)	(99,000)
Experimental and special	(5,800)	(8,000)	(10,000)	(12,000)	(13,500)	(15,000)
Inservice	[1] 6,850	5,218	5,500	6,000	6,500	6,500
Continuing education	2,800	5,500	8,000	10,500	13,000	15,000
Scientific evaluation	150	194	200	250	250	250
Dependency allowances		4,000	4,500	5,000	5,500	6,000
Total	[1] 94,448	114,412	133,200	152,250	170,250	187,250

[1] Includes $2,182,000 comparative transfer of funds for inservice training in mental retardation.

B. Fellowship and Research Career Programs

The fellowship program was similarly projected in 1963, with budget allocations reaching $18 million in 1973. Here, too, annual increases have not kept up with need. The original projection had shown a level of support of $13 million by 1967, rather than the present level of $9,133,000. In addition, the research career program, as already described, represents a major additional program emphasis.

Table 12 shows the projected needs for both the research fellowships and research career programs.

TABLE 12.—*Fellowship and research career programs budget needs*

[Dollar amounts in thousands]

	Number of awards	Amount
Fiscal year 1968:		
Research fellowships program	1,400	$8,280
Research career program	192	4,310
Total	1,592	12,590
Fiscal year 1969:		
Research fellowships program	1,900	10,795
Research career program	224	5,154
Total	2,124	15,949
Fiscal year 1970:		
Research fellowships program	2,285	14,367
Research career program	261	6,052
Total	2,546	20,419
Fiscal year 1971:		
Research fellowships program	2,735	15,899
Research career program	299	7,213
Total	3,034	23,112
Fiscal year 1972:		
Research fellowships program	3,240	18,849
Research career program	336	8,131
Total	3,576	26,980

RESEARCH GRANTS

Mr. FLOOD. $4,846,000 of the requested increase is for research grants to support 151 more projects in 1968.

NARCOTIC ADDICT REHABILITATION ACT

You have a new item which you call "Research projects under the Narcotic Addict Rehabilitation Act, $504,000." How is that any different from the research you are doing under what you call "Narcotics and drug abuse"? What is the difference?

Dr. YOLLES. They are related. The projects to be included under this item are field surveys, pilot programs, field testing, and determination of the numbers of addicts in the United States. These field studies are specifically mentioned in the legislation. They will serve as the basis for distribution of support for construction, operation, and staffing of facilities.

METROPOLITAN MENTAL HEALTH PROGRAMS

Mr. FLOOD. You are requesting an increase from $371,000 to $950,000 for what you call metropolitan mental health programs. What is this research? Why must you have an increase of this proportion?

Dr. YOLLES. This is a new item. It is a new program which has recently been established, and we are trying to develop some research grants and program efforts in this area.

One of the items which has been very evident in past years is that the problems faced by metropolitan areas for the delivery of mental health services are somewhat different than those of the States. We have been dealing with States for the most part. The new center for

the study of metropolitan and regional mental health programs will try to determine through research grants, contracts, and other support some of the special needs and some means of dealing with the special needs of metropolitan areas for mental health service programs.

TRAINING GRANTS

Mr. FLOOD. You have an increase of $8,496,000 for training grants. This would support 2,210 grants compared with 2,023 this year. To whom do you make these grants? What are you buying?

Dr. YOLLES. We are buying the production of manpower in these grants. We are buying the support of departments to produce manpower. All such applications come into the Institute and are reviewed in the usual double review fashion by a group of peers of the people who are applying. The people who apply are usually universities or other training centers. They apply for grants to support their operations, for stipends for trainees, for special pilot programs, for training of general practitioners in the short courses and a whole variety of training programs.

Mr. FLOOD. Do you make an effort to interest general practitioners in refresher courses in this general area?

Dr. YOLLES. Yes, sir, we do.

Mr. FLOOD. Are they interested in it?

Dr. YOLLES. There is a tremendous amount of interest. We have trained about 11,000 general practitioners so far. About 11,000 general practitioners have taken short courses which have been supported by the Institute. One of the items that we hope to introduce as a new part of our program is continuing education, to refresh the knowledge of some of the mental health professionals who have been out in the field for some time. There is a need in the field for this at the present time.

STUDIES OF SCHIZOPHRENIA

Mr. FLOOD On page 26 of your justifications you give a little detail on what you call the newly developed center for studies of schizophrenia.

Dr. YOLLES. Yes, sir.

The center for studies of schizophrenia again is the result of the reorganization of the Public Health Service and of the Institute in recent years. Schizophrenia is the core problem in mental health today. About half of all the beds in the hospitals of the United States are occupied by schizophrenics.

Mr. FLOOD. What is a schizophrenic?

Dr. YOLLES. A schizophrenic is a person who is suffering from a severe mental illness which is characterized by a dissociation or fragmentation between the emotional parts of his personality and the intellectual parts of his personality.

Mr. FLOOD. Is he a dangerous person?

Dr. YOLLES. Not necessarily. In some types of cases, a type called paranoid schizophrenia the individual may be convinced, may have a delusion that he is being persecuted or that someone is after him and will try to strike back and prevent the supposed assailant from getting at him. This occurs only in very small numbers and relatively infrequently.

Mr. FLOOD. I would ask more about this but you have a rather detailed special statement and we will place that in the record.

(The statement follows:)

SPECIAL REPORT: SCHIZOPHRENIA

INTRODUCTION

Schizophrenia is among the most dreaded diagnoses in medicine. Patients suffering from its variety of strange and often crippling symptoms now occupy more than half of the mental hospital beds in the country. Data from the Biometry Office of the National Institute of Mental Health indicate that three-fourths of our schizophrenia victims were afflicted during their most formative and productive years, between ages 15 and 44. Unfortunately, the illness has been on the increase among pre-adolescents and young adults during the last decade. Only about a third of these people recover. Despite new drugs, improved therapies and community rehabilitation programs that allow patients to leave the hospital, most of them do not return to normal life in the manner of a convalescent from organic illness, but remain in a limbo of the maimed. In the United States and the rest of the world schizophrenia remains a major public health problem.

Like cancer, schizophrenia poses baffling and fundamental questions to those who would understand its etiology and reduce its prevalence. This NIMH objective requires a convergence of researches, since the origins of the illness are thought to lie in biochemical and phychological, social, or genetic mechanisms perhaps in some combination. Thus investigations of social and family disorders as well as biochemical and organic studies tend to be integrated in current research programs. At the same time, the Institute has sponsored the application of new findings and drug treatments, and intensified community services, which have improved the early detection, treatment, and rehabilitation of schizophrenic patients. During the past year, as in the year before, these programs had a small but palpable effect, and state and community mental hospitals saw a drop of 15000 resident schizophrenics.

This report will summarize the Institute's program which is devoted to the conquest of schizophrenia through support to a wide range of researches and to studies and service programs that apply new findings in institutions and the community.

RESEARCH PROGRAMS

Scope

The NIMH research grant program, from its inception in 1948 until the end of fiscal year 1966, included over 2800 awards, amounting to nearly 100 million in studies related to schizophrenia. This is about a fourth of the entire NIMH program.

During fiscal year 1966, over $18,539,000 was devoted to research activities on schizophrenia through projects within the intramural program as well as research grants. During the year the Institute supported more than 400 projects relating to schizophrenia, ranging from small pilot studies to the diverse activities within large clinical centers.

In 1966 in order to coordinate its many programs, to collaborate with outside institutions and to prevent duplication, the Institute formed a Center for Studies of Schizophrenia. It will serve as a center for professionals in both treatment and research assuring a better exchange of information about schizophrenia, stimulating programs of research, service, and training, and evaluating current developments.

Biological studies

Although a number of biochemical and biological studies, to be recounted here, show new and interesting avenues toward an understanding of schizophrenic illness, it should be emphasized that these are only a fraction of the basic researches receiving Institute support which can be expected to have important bearing on schizophrenia. The following are recent developments specifically oriented to schizophrenic phenomena, among them two promising possibilities in the biochemical area: the discovery that some forms of the disease may be associated with an error in metabolism (transmethylation) and the detection of an abnormal protein in the blood serum of some schizophenics.

Two years ago an NIMH grantee generated great scientific interest in the process of transmethylation when he discovered a chemical in the urine of some

schizophrenics not found in the urine of normals. A subsequent assay by an independent researcher of a large and mixed group of people corroborated the finding. The compound, which shows up as a pink spot on an analytical test, is known by its abbreviation as DMPEA (3,4 dimethoxyphenylethylamine). It is a doubly methylated derivative of the normal body chemical, dopamine, and a close relative of adrenalin. But DMPEA has a structure similar to that of the hallucinogenic substance, mescaline. The difference between the DMPEA molecule and that of dopamine lies in the added groups of atoms known as methyl groups.

A very slight error in the body's process of transmethylation could transform the normal dopamine into a substance resembling mescaline. There is still no direct evidence that such a metabolic flaw is responsible for symptoms of schizophrenia. Nonetheless, such a flaw seems at least possible, and if an error in transmethylation were found to exist in schizophrenia, it would open up the possibility of finding chemicals to correct the error in metabolism, thus hopefully counteracting the symptoms. Some scientists are eager to begin such a search, but there is considerable basic research to be done first. The discovery of DMPEA in schizophrenics' urine sparked what is presently a most intensive exploration of the chemistry and metabolism of adrenalin and related substances.

While many investigators have concentrated upon adrenalin metabolism and the potentialities of transmethylation, others have been focussing upon serum proteins. Recently, an NIMH research team detected an abnormal protein in the blood plasma of schrizophrenic patients. Its meaning was unclear, but a number of independent researchers have since found that this protein was present in the plasma of schizophrenics to a greater extent than in normals. When the fraction was injected into experimental animals it altered behavior. It changed cell metabolism and oxidative processes in other studies.

There is continued research in the purification, isolation, and identification of these active blood substances. Once again, the discovery of an apparent abnormality will necessitate considerable basic work before its significance can be interpreted. It is not known, for example, the extent to which this abnormal blood factor is specific to schizophrenia, rather than representing a product of generalized reactions to stress. However, the discovery has had some interesting value in clinical studies.

In one Institute study of twins who are discordant for schizophrenia, biochemists have been able to distinguish the schizophrenic from the non-schizophrenic twin accurately on the basis of the serum protein factor. Moreover, another study indicates that there are detectable differences between schizophrenics in whose blood the protein is found, and those who do not seem to exhibit the factor. The differences appeared in their conditioned galvanic skin responses, tests of position sense, and brainwave responses to visual stimulation. The schizophrenic patients who did not show the factor had different sleep patterns, and indeed they seemed to have come from less stable families, and to have showed more severe personality disturbances prior to the onset of diagnosable illness. Perhaps their illness was more psychologically determined than the illness of patients showing the blood factor. Schizophrenia does not appear to be a unitary disease, and the abnormal blood factor may provide one biochemical test that will distinguish between two groups of schizophrenics with characteristically different behavior and histories.

The way in which this serum factor might influence mental functioning has become the impetus for continued research. One Institute team has found that it alters the rate at which certain amino acids penetrate the walls of red blood cells. The membrane permeability is associated with a change in cell metabolism. The manner in which the protein factor affects the permeability of the blood brain barrier, for certain amino acids, will provide one link explaining how an abnormal blood protein can affect brain biochemistry, and thus mental function.

Other clues to possible biochemical abnormality in schizophrenia have been detected in the perspiration of psychiatric patients. One NIMH grantee has found and synthesized a fatty acid that appears to be responsible for the distinctive odor of the sweat of schizophrenic patients. The investigators are currently trying to determine the biological significance of this finding.

It seems probable that metabolic factors in schizophrenic psychosis will continue to be detected in a number of forms, although it is too early to see how these products are related. More than one NIMH supported study has focussed upon clues to be found in periodic catatonia. Some patients swing, with almost clocklike regularity, from a state of excitement or normalcy into degrees of stupor, and inactivity. Each of these patients is studied in both states, and com-

pared with himself. The investigators report that there are distinct metabolic differences between the two states. Some investigators have found thyroid medication helpful.

A possible metabolic defect asosciated with schizophrenia has been noted from another level of observation. In biochemical studied of twins at NIMH only schizopherenic twins showed a lactate pyruvate ratio thought to indicate an abnormal blood protein, and also a lower protein-bound iodine which is a measure of thyroid hormone. There was a high incidence of thyroid disease in the parents of these twins.

Another study of acute psychotic disorders within a carefully controlled metabolic ward is integrating physiological observations. The investigators believe they are obtaining new information about the significane of amines in schizophrenia. The amines are a class of compounds containing many psychoactive substances, such as the catecholamines so important in brain activity.

Within the Laboratory of Clinical Science at NIMH the cyclic psychoses are being studied with an eye to the biochemical changes concomitant with the dramatic emotional shifts of these patients. In this integrated approach emotions can provide interesting clues, and one curious observation to emerge from recent research on schizophrenia is that remission is commonly attended by depression.

Improved instrumentation has permitted investigators to study biological and physiological concomitants of the illness by other than biochemical methods. Brainwave patterns have been obtained from the surface of the head, permitting comparisons of normals, neurotics, and psychotics. EEG studies, together with assays of drug responses, have suggested that schizophrenics may suffer from a sustained state of hyperarousal. Sleep studies also suggest that the mechanisms relating to rapid-eye movement sleep, and associated with dreaming, are affected by some schizophrenic illnesses, and perhaps certain phases of the psychosis.

Examined with respect to this phase of sleep, differences have been observed between those schizophrenics showing an abnormal plasma protein, and those who do not.

Computerized observational studies and the development of biotelemetry instruments are being prepared for a large study of a patient population. At present behavioral observations are amenable to computer analysis. Soon there will be simultaneous and continuous physiological recordings. Studies of periodic catatonia, of 48-hour manic-depressive cycles, and recent researches into biological rhythms suggest that factors of internal body timing may be a relevant path of exploration in understanding biochemical and behaviorial abnormalities of schizophrenia.

In a great many of the current studies, recent developments in instrumentation have made it possible to ask questions about the relation between biology and behavior that were unanswerable by earlier techniques.

Psychological, social, and environmental factors

The new instruments and sophisticated research of the last few years inevitably have complicated theories on the origins of schizophrenic illness. Subtle biochemical aberrations have been detected, suggesting that biological abnormality might be responsible, at least among some groups of psychotics. At the same time, laboratory studies have been emphasizing the unity of mind and body, indicating how learned behaviors and emotional stresses can alter body chemistry and then again, in turn, influence subsequent mental states. Thus many researchers have invested in a multifaceted approach, exploring the psychodynamics, social environment and physiological factors of schizophrenia. It has become clearer, in the last few years, that psychological and social factors bear some heavy weight in the development of this devastating psychosis.

Studies of twins, and studies of family behavior have proven extremely revealing. A classic study of identical twins indicated that if one twin developed schizophrenia, there was an 85% chance that the other would also succumb. But there are many instances in which only one twin becomes schizophrenic. NIMH scientists have studied 15 such pairs, in an attempt to discover why one became psychotic while the other did not. They found that the infant, who was to develop schizophrenia, weighed less than his twin at birth. During childhood he tended to be less organized and competent, less capable of sustaining any goal-directed activity. He was the more sensitive, more anxious of the two, and the least happy. Differences on biochemical tests raised suspicion that he was biologically weaker. There was some evidence that this twin inspired in his parents an overanxious protectiveness greater than that if his co-twin. Other, recent studies of fraternal twins have shown developmental histories

similar to the identical twins. The investigators concluded that a disturbed family background was critical to the development of the psychosis, whether the twins were genetically identical or different.

The analysis of the disturbed family has been an area of great advance in the last year.

An NIMH scientist who has been probing the process of schizophrenia in relation to the family of the afflicted performed an important replication last year of an earlier study. "Blind" judges were able to correctly select from a pool those families containing a schizophrenic child, a judgment made entirely from seeing the family's modes of communicating and interacting. Methods for studying families have been refined and are invaluable to researchers around the country.

Even if the preconditions for schizophrenia prove to lie in biological vulnerabilities, other NIMH studies are displaying the important role of learned communications patterns. At Yale University, a longitudinal study of schizophrenic's families has led scientists to the conclusion that the parents by their manner of communication created a conceptual environment in which the children were essentially trained in irrational thought processes. The researchers found that the pathology of the families was so notable that the psychiatric illness of the offspring would have been understandable on purely environmental grounds.

Processes not well understood two decades ago are now being probed in a number of studies comparing the behavior of families in which there is a schizophrenic child with those having normal offspring. Retrospective interviews with psychiatrically disturbed soldiers, have suggested a correlation between their disturbance and the rejection and hostility of their fathers. Indeed, case studies have indicated that patients who reported a positive relationship with the parent of their own sex also showed a more rapid recovery. Similarily, in other studies researchers reported that males who recovered described their fathers as more dominant in the family than did patients who became chronic. Although earlier theories stressed issues of dependency and parental domination, and a psychoanalytic concept of faulty development, current work indicates that both parents share in the responsibility, and focusses on the pathological thought and communication processes common to parents and offspring.

Some of this research has been conducted by recording and filming family discussions within the laboratory. The family is asked to decide some question, and both the family discussion and individual opinions are studied. Such work has led to a recent emphasis on family therapy, for a number of researchers have found that communication processes within the family improved by treating the family unit, which, in turn seems to help the patient. The potential of family therapy becomes more emphatic in view of the mounting evidence.

The family communication patterns have been strikingly consonant with the condition of the patient. Withdrawn schizophrenics have emerged from families that handled communication in a very amorphous fashion. Schizophrenics who were eruptive, over-reactive or had blatant delusions grew up in families where ideas were clearly expressed but subsequently acted upon in a way that distorted them or negated them. If the correspondence between a patient's symptoms and his family's communications patterns were to obtain in other cultures, researchers could be more certain that family communication specifically shapes schizophrenic illness, and that the correspondence found in the United States is not relevant only to our culture. Institute supported studies, in Lebanon and Japan are concentrating upon verbal interactions, and other cross-cultural studies are under way.

Recent work by NIMH researchers now makes it possible to conduct studies of family communication in a relatively standard way, and reliable categories have been evolved for scoring communication abnormalities. Thus the investigator can make reliable distinctions between schizophrenic and non-schizophrenic families, and can accurately use Rorschach results to match up a parent with his schizophrenic child.

Perception and intelligence

The symptoms of schizophrenia, in all their baffling diversity, have begun to yield clues to certain fundamental changes in the mental functioning of the sick individual. Some patients experience harrowing changes in perception, seeing the world as through a distorted glass, finding that colors are unduly brilliant, or peculiarly dull, that objects look two dimensional. Smell, taste, and touch may be altered. Frequently there are auditory illusions, voices in the head, and while some victims report a frustrating slowdown in thinking, others find their

minds are racing too fast. Emotionally, too, there is strange diversity, and while some people are suspicious, or fearful, or depressed, others become mute and withdrawn, apathetic, indifferent, or even instances, giddy.

A number of investigators conclude that the primary characteristic of schizophrenia is a form of thought disorder. The ill person often tends to express himself in a disorganized way, showing a kind of fragmentalization, and loose associations. Delusions, long observed in the clinic, are just now being given detailed examination in the laboratory for insight into the nature of the patients' cognitive deficit. Other research teams, supported by NIMH, are studying the flaws in attention and perception now widely attributed to schizophrenics. For example, one group is studying the orienting reflex, which has to do with an involuntary shift of attention in response to a new event. Considerable work on the orienting reflex in animals has been accomplished through the study of EEG patterns that reveal attention responses of the brain even when an animal gives no behavioral reaction.

Perhaps it should not be surprising that a number of NIMH supported studies have recently indicated that schizophrenics suffer decrements in intelligence long before the overt onset of illness. Indeed, a current review of the childhood I.Q. scores of schizophrenic patients may lead to new methods for detecting the illness at a very early stage, before breakdown, perhaps through serial intelligence tests.

One study has compared the intellectual processes of three kinds of patients: schizophrenics who were notably disordered in childhood, schizophrenics whose disturbance appeared in adulthood, and patients with other psychiatric ailments. The most impaired were the people who had suffered schizophrenic disturbance in childhood. Schizophrenics with childhood symptoms exhibited lower I.Q., impaired social skills, and reduced perceptual abilities. Typically they had poor memory and thought disorders. The people whose disturbances occurred earliest in life showed significantly poorer perceptual functions than those in whom disorder occurred later.

Recent evidence from another quarter suggests that the intellectual loss of the schizophrenic is associated with the disease process. Here, in a carefully controlled study the investigator examined I.Q. scores from children who became schizophrenic as adults. These children had shown a decline in I.Q. as they progressed from early to late childhood. Their I.Q. scores were significantly lower than those of their peers or normal siblings, yet they had not been considered psychotic or even disturbed at the time.

The investigators felt that this decrement in intelligence indicated that schizophrenia must have its roots in childhood, many years before recognizable symptoms appeared. They felt that internal stresses, unperceived by outsiders, were already draining off intellectual resources necessary for optimum performance. These results cast into doubt the assumption that the low I.Q. scores of adult schizophrenics derive from their low socioeconomic background or rearing in low-intellect families.

A number of other studies may bear upon the issue of intellectual decrements among schizophrenic patients. One investigator is conducting a series of studies on the verbal behavior, and influence of operant conditioning on speech patterns in normals and schizophrenics. This work may reveal something about the nature of the communication problem in the schizophrenic, and the biological basis of speech. Moreovore, the work has implications in training regressed patients. Possibilities for therapy have been seen as these operant techniques have been applied to children, for example an unresponsive, unspeaking youngster who was subject to tantrums showed an increased rate of vocalization and even shaped words as a result of training, which also caused her to respond to verbal commands and controlled her tantrums during experimental sessions.

Over several years, other investigators have concentrated upon the emotional disturbance typical of schizophrenia, and an effort is now being made to classify and measure disturbance of feeling through the responses of patients to selected pieces of music.

One NIMH laboratory is devoting attention to studies that may elucidate the deficits of perception, of attention, and problem solving, observed in so many patients. Members of this group hope to discover how the schizophrenic's poor performance on tests may relate to psychological arousal. Schizophrenics, as a recent study shows, require an unusually long response time if they are asked to judge the speed of a moving visual stimulus. Still, their undue response time does not seem to stem from misunderstanding the task, from lack of motivation, or inattention. In order to explain their apparent slowness of perception, the

research team has found it necessary to do basic work on perception. One study, using schizophrenic twins and their normal co-twins, is concentrating upon the performance deficit as related to indicators of arousal in the autonomic nervous system. As experimental findings in the literature are synthesized with data from this laboratory, it is clear that the psychology of the schizophrenic differs sharply from that of the non-schizophrenic, showing a fragmentation that, defies easy theorizing.

Genetic and Sociological Factors

The roles of heredity and environment in schizophrenia are difficult to disentangle. An early study of identical twins indicated that, if one twin suffered from the illness, the other twin was extremely likely to have the disorder. Scientists at NIMH have had a unique opportunity to study the weight of heredity and upbringing in four young women, who are identical quadruplets, and the first recorded case of quadruple schizophrenia. A book, *The Genain Quadruplets*, reports some of the findings of this multi-discplinary study, which is still in progress. As a team of doctors studied the girls they saw that they shared an abnormal brainwave pattern, one exhibited by their father in whose family there was evidence of mental illness. In addition to suspicious genetic factors, however, there were also environmental abnormalities. The parents were suspicious, prevented the girls from having friends, and established a constrictive regimen. From a very early age the quadruplets evinced signs of a constrictive nature, and during their illness they showed catatonic symptoms. Thus the study suggested an interaction of inherited and environmental forces that allowed schizophernia to develop, and shaped the manifest symptoms.

A massive study of over 3,000 schizophrenic cases has been undertaken by one laboratory. Here, investigators are comparing the mental and physical status of children who have schizophrenic parents with children of non-schizophrenic parents. The life-expectancy of these subjects is compared with that of the general population, as is the incidence of mental and physical illness in siblings. If one compares schizophrenic patients of the 1930's with those of the 1950's the study indicates that marriage and fertility rates have been on the rise among these schizophrenics. There is also an increase in the number of marriages that terminated in divorce or annullment or separation, and in the proportion of second and third marriages. This suggests that there is a growing population of children for whom one or both parents are schizophrenic.

Clues to possible genetic factors in schizophrenia lie in the statistics of large population studies. One extensive survey includes 97 family groups (about 17,707 individuals) in which there are eight generations under evaluation at present. From these various studies it may be possible to answer some questions about the incidence of mental and physical illness as heritable factors.

Perhaps the most accurate information presently available on the rates of mental hospitalizable illness come from Norway, where there has been a national registration of mentally ill persons since 1916. There a current survey will cover all persons who were admitted to a mental hospital for the first time, between 1938 and 1962. Other studies of psychosis rates are being conducted in underdeveloped countries, there, the assays suggest there may be a seemingly low incidence of psychiatric illness simply because fewer people are hospitalized and there are large numbers of psychotics living within their communities. Within Canada and the United States investigators are currently looking to see how psychiatric disorder may be related to various socio-cultural factors, in both cities and farm communities.

A 10-year follow-up study of schizophrenic patients in the New Haven area in Connecticut has indicated that there is a complex relationship between social class and rehabilitation. Patients from high economic levels, with high educational and occupational status, were more likely to be released from the hospital to work outside and receive outpatient treatment than were the patients from lower socio-economic backgrounds. At the same time, these released patients from higher social class were not functioning at a level so close to normal counterparts, as were the lower class schizophrenics. The ability of an upper class patient to remain outside the hospital may not indicate greater improvement or even adept social performance, but such factors as the willingness of his family to accept responsibility for him.

A curious finding, replicated by Institute researchers comes from several populations of schisophrenic patients in the United States, Japan, Lebanon and Formosa. Birth order appears to be related to the illness, and youngest daughters surveyed appeared to be most likely to be schizophrenic.

In attempts to understand genetic and social factors in etiology, one researcher is studying adopted children and another is comparing Israeli children raised by their parents in town with those raised in a Kibbutz.

One of the difficulties of attempting to decipher the socio-environmental factors in schizophrenia, judged by hospitalization, is that different communities and their distinctive attitudes toward the mentally ill can, in part determine whether patients will be able to leave the hospital and function outside it. Current surveys of community attitudes toward mental illness, and studies of the hospitals' criteria for admitting patients, may help to clarify these issues.

Comparisons between psychotics and other groups are now being made among four Western European psychotic populations, using an American patient assay and its data in addition to such factors as social class.

Ethnic groups within the United States are being explored for clues to what may be different incidences of schizophrenia. The reseachers also wonder if there are ethnic differences in a family's response to psychosis in one of its members.

Although it has been estimated that one out of every hundred persons in the world will suffer schizophrenia at some time in his life, diverse criteria for diagnosing, treating, and indeed counting persons with the illness have led to some confusion and disagreement. In the last year a collaborative study was developed with the World Health Organization, and launched by a grant from NIMH toward the initiation of an international pilot on schizophrenia. Scientists participating will attempt to devise and apply standard research techniques and methods for identifying schizophrenics and their behavioral symptoms. The teams will assess the effects of cultural and social variables in the course of the disease. They will be working in widely different cultures in the eight participating Nations: United States, Russia, Denmark, Great Britain, Colombia, Nigeria, India, and Nationalist China. As part of a world wide mental health program, schizophrenia was picked for first study because of its frequency and severity the world over.

An interview developed at NIMH and translated into the relevant languages will be a major instrument in screening potential subjects at field stations in each country, and the first object of the endeavor is to devise uniform psychiatric screening methods. Each field station will admit a specified number of psychiatric patients for intensive study.

The NIMH screening interview has already been used in Sweden and is being used presently in Taiwan. Data from these field stations will be compared with information from a Japanese and a U.S. group, and may help to reduce confusion over diagnosis, the natural history of the disease, and response to various treatments. It may lead to a means of answering unresolved questions about the incidence of "borderline" psychoses, their relation to schizophrenia and to the pressures of modern urban living. Future studies may tell whether particular cultures are especially conducive to schizophrenic psychosis.

Childhood schizophrenia

Childhood Schizophrenia is a growing health problem. While hospital populations of older patients have declined there has been an annual increase in the number of youngsters admitted for schizophrenic disorders. This rising incidence may reflect improvements in diagnosis and the availability of child clinics. Whatever factors underlie the current figures the challenge of childhood schizophrenia has become a major one. Failure to cope with it can mean entire lifetimes ruined.

Moreover, the methods developed to study adults are not adequate for children, so that the study of the phenomena in childhood presents new problems. Childhood schizophrenia is often marked by withdrawal from reality, failure to learn language, and unmanageable behavior. As one might expect, the illness often prevents a youngster from learning basic intellectual and social skills. An early form, known as autism, describes those poignant and perplexing youngsters who seem to live in a world of their own, uninterested in their environment, and unreached by their parents and the people around them.

EEG tracings from autistic children have been studied recently for distinguishing abnormalities. In a large group of disturbed youngsters the researchers found that over half of them had abnormal EEG's by comparison with the EEG's of a normal control group. These unusual brainwave tracings were most prominent during the transition from waking to sleep. Only further study will reveal whether the psychosis is primarily a function of organic abnormality, or whether it might be the result of prolonged anxiety, perhaps related to environmental background.

Up until a decade ago little was known about this tragic disorder in youth. A study that gives every promise of materially increasing our knowledge has been started in a special children's ward within a research center in Indianapolis. There, children live for several months at a time, visiting home frequently. The grantees are investigating social interaction among these children, motor development, sleep and dream behavor, and are studying their families in detail. A variety of methods include operant conditioning and the analysis of evoked brainwave responses. Dietary intake is being examined closely, and biochemical tests are being analyzed. Operant conditioning techniques, used in a number of studies, are also showing a potential usefulness in developing the verbal skills of these sick youngsters. Family studies are also beginning to reveal communication patterns between pre-school youngsters with schizophrenic psychoses and their parents. At the present time an exploration of a possible chromosomal defect has not offered any positive evidence that would permit chromosomal detection in infants.

DIAGNOSIS AND DRUGS

Since 1955 the number of patients in our public mental hospitals has been going down, at about one percent a year. These discharges reflect the success of transquilizer therapy and community rehabilitation programs. If discharges are increasing, so too are new admissions, particularly among young people. The increase in childhood schizophrenia may also reflect improvements in the detection of diagnosis of schizophrenia.

In part because the symptoms of schizophrenia are so diverse, many investigators refer to the schizophrenias considering it a constellation of illnesses rather than a unitary disease. Quite a few grantees have been exploring the important and difficult job of diagnosing and differentiating at an early stage in disease. The job has become more difficult, ironically, as social attitudes toward mental illness have become educated. Today's patient is likely to enter the psychiatrist's office without the grandiose delusions, or classical syndromes that marked the unmistakable schizophrenic thirty years ago, and for the simple reason that he arrives earlier in the progress of the disease. As current research has emphasized, sleep disturbance is an early harbinger of psychotic breakdown: thus as clinicians become acquainted with the meanings of various kinds of insomnia, they are alerted to early signs of mental illness. Research on sleep patterns has also suggested a distinction between two kinds of schizophrenics.

A number of studies currently devoted to diagnostic differentiation in psychosis, are drawing upon a battery of objective test measures. One research team is attempting to validate objective test measures for ten separable syndrome factors of the In-Patient Multidimensional Psychiatric Scale.

New prospects in diagnosis lie over the horizon as a result of research on biochemical differences between schizophrenics and normals, and it may someday be possible to apply a simple blood test or urine test, akin to the detection of PKU in infants.

Studies of the efficacy of drugs are also leading to differentiations among schizophrenic patients. NIMH, in a program of special collaborative grants with hospitals, has been sponsoring a large scale and integrated program to evaluate subtle differences in treatment on huge numbers of patients. Last year, in two of these studies, the grantees were focusing on acute schizophrenics who had just been admitted to the hospital, and the goal was to predict response and match the right drug to the right patient. A validation study has followed.

There is no doubt that tranquilizing drugs, notably the phenothiazines, have proven effective in returning patients to the community and reducing the likelihood of relapse and re-hospitalization. They have permitted the maintenance of some patients in the community without any hospitalization and have produced rapid improvement in those patients who were hospitalized.

The efficacy of drug therapies, as tested and validated by NIMH supported grantees, is also enhancing a more refined and efficacious use of drugs. One grantee in Ohio, for instance, reports that visits to the home by public health nurses can enhance the value of drug treatment and avert hospitalization. Similar reports from other studies have encouraged the NIMH Clinical Neuropharmacology Research Center to determine whether home visits by a psychiatrist-supervised nurse will permit a better regulation of drug dosage and deal more effectively with family problems than the vists of a released patient to a formal outpatient clinic.

A large collaborative study, involving seven hospitals, has been evaluating the value of massive doses of phenothiazines in moving chronic patients toward

discharge. This study led to a very new and sensitive method for determining whether a patient was ready for discharge, and it also brought to light some previously unknown side-effects. Last year, as a result, grant supported studies were initiated to investigate opthalmologic changes following massive doses of phenothiazines. The work has brought to the attention of clinicians an unforeseen complication in this kind of drug treatment.

The pharmacological studies in schizophrenia last year covered a huge range. One study began to evaluate the efficacy of allowing doctors to tailor drug mixtures to the patient's needs, and other researchers tried new drugs on schizophrenics who previously did not respond to drug therapy, attemping to predict their response to the new compounds.

Other studies utilized behavioral measures to detect drug responses, while biochemical studies focussed on the use of drugs to induce model psychosis. Still, others proved the possible alteration of thyroid function induced by psychotropic drugs, and hormonal factors that may interact with tranquilizer metabolism.

Collaborative studies of the phenothiazine drugs have continued, and data collected to date still indicate they are the treatment of choice in schizophrenia. A new phenothiazine, acetophenazine, has been producing more clinical improvement than fluphenazine. Fluphenazine enanthate, a long acting preparation that can be injected, is under scrutiny in several studies. Because it can be injected and is long lasting, it may have practical advantages, saving nurses time on chronic wards, and insuring that released patients get their medication.

Drugs, similar pharmacologically to the phenothiazines, are being studied by grantees: they are thioxanthines and butyrophenones. A question now under study is whether patients will do better on one of these classes of drugs than the other.

Other researches on background factors in schizophrenia are proving to have prognostic value. One group has found that a favorable outcome can be anticipated if the adult patient is married, extroverted, showed adjustment before a sudden onset of illness, if he is emotionally responsive, and there were demonstrable factors such as severe stress precipitating his attack. Remission is also enhanced by the attention and help a patient receives in his community when he is discharged from the hospital.

HOSPITAL IMPROVEMENT PROJECTS AND INSERVICE TRAINING GRANTS

Through its hospital improvement program the Institute has been helping the State mental hospitals to enhance their therapies and prepare schizophrenic patients for discharge and placement in the community. A pilot screening of chronic wards in one hospital indicated that about 50 percent of the patients might be discharged and maintained in their community with proper help. Prior work with the patients' families showed that they were willing to come to the hospital and learn how to deal with a mentally ill relation. Patients were involved in group therapy, vocational training, and patient self-government was encouraged.

In the three years of the Hospital Improvement Programs, half of the State institutions have initiated projects and 182 have received inservice training grants. Funds have been used to help change the hospital so that it could acquire a therapeutic rather than a custodial climate. Some hospitals have used grant funds to enable their patients to return to the community, by establishing halfway houses, foster homes, or developing hospital after-care services.

In one project, patients work in hospital industry, and the work situation is used to enhance group therapy. Over 450 patients are assigned to hospital jobs, and for each ten patients there is a trained staff member who provides group therapy.

Another hospital has established a special unit for chronic patients prior to discharge. There staff technicians help patients in grooming, etiquette, in vocational training, discussions of current events, teaching them the skills they need, how to prepare a meal, use a telephone, drive an automobile, shop, and hunt for jobs.

With NIMH aid, a unique program has been instituted at Patton State Hospital, which serves a large population of 4600 patients. Here, many of the physical facilities are obsolete and an effort is being made to reduce the patient population by 1500 over a five year period. The program to accomplish this goal involves the training of families, or of persons willing to serve as surrogate family members. These people learn to care for chronic patients who

no longer need intensive treatment. With proper help about 50 percent of these patients might be discharged and placed in the community. Family members, employers, and family surrogates such as ministers or lawyers are trained to treat the patients.

The patients, about sixty at a time, come from their own wards to a special center, which operates as a day hospital. The family's education begins in group preceptor programs. The families are instructed by films, and lectures on the dynamics of mental illness, and principles of psychology. They work with their schizophrenic relatives and with non-related patients in the center. At times the hospital patients act as observers during the group programs of their relatives, in a system of mutual help and instruction.

APPLIED RESEARCH DEMONSTRATION PROJECTS: PREVENTION AND REHABILITATION

Two decades ago the popular view of the mental patient was that of a disheveled, incoherent, almost sub-human creature in a miserable asylum that was no better than a prison in many respects. During the last 20 years this concept has been vanishing. Indeed, many of the deteriorating symptoms once blamed on mental disease, are now believed to have been the secondary effects of isolation and hospitalization. By comprehensive community mental health programs professional workers are encouraged to prevent hospitalization where possible, and to reduce the time that a patient must spend within a mental institution. NIMH, in 1956, established its Mental Health Project Grant Program to enhance this trend, helping individuals to remain within their communities by early action, and to remain there after discharge from a hospital.

One study reported 95 percent success with 75 families, in which an acutely ill member was able to avoid hospitalization through the intervention of family treatment. In Pennsylvania, the families of more than 50 schizophrenic patients were given weekly therapy sessions, and in the majority of cases it was possible to avoid hospitalization. Only two patients out of fifty were institutionalized and then for only a brief period. Family therapy allowed one adolescent to return to school, and in general promoted improved relationships within the family with perceptible benefits to the patients, who came from all socioeconomic levels. In another center, home management was effective in treating severely disturbed children.

By the development and use of community resources, other grantees avoided the expense and the separation of schizophrenic children from their families Undergraduates from a local college acted as companion counsellors to the children, visiting them at home four or five times a week for an hour or two. The college students have been supervised by staff members at the child guidance center. These professionals are consultants to the whole community, and one function they serve is to clarify misunderstood behavior on the part of schizophrenic or disturbed children, and educate the community in their special needs. So far the community experiment indicates that schizophrenic children can remain in the community and that their non-professional companion counselors function very capably without much preparation or supervision. This is a promising innovation in the use of community resources.

Another approach is being used in treatment of preschoolers by group psychotherapy. Psychotic school children, aged 6–10, are also being helped within the public school classroom. This novel project is now in its second year. The normal children are taking care of the schizophrenic children, who spend a part of the day in regular classrooms. Not only does each disturbed group have older students assigned to look after them, they have especially bright children as tutors. Thus, bright second and third graders read to the younger children, and help the troubled child to focus on school material. The school principal and teachers have noticed that the project children react well to their peers, and that the normal kids make an effort to include them in games and activities.

Psychotic children, under thirteen, are also given comprehensive day-care and multi-dimensional treatment in another community where the community agencies are involved in diagnosis and have been educated in the management and treatment of emotionally disturbed children.

In another project in New York, it was possible to rehabilitate young adults so severely ill that they would be rejected by the usual community facilities. Eighty percent of these patients successfully made the transition from hospital to school, or a job, or home responsibilities. The transition was effected in a sheltered workshop program, whose success doubled the original expectation for this difficult group of patients.

Follow-up clinics and non-professional aides have been effective in a number of locales. One study indicates how a comprehensive rehabilitation program can work in a city slum; and in the rural area of Appalachia, where discharged patients no longer return in such numbers to the hospital owing to the help of follow-up clinics. Visits from clinic teams have aided a quarter of the patients who cannot get to the clinic for help because of distance and poverty.

These innovations, in the approach to preventive or rehabilitation treatment, removing some of the stigma and pain from mental illness. Not only do these community programs enable patients to remain outside the hospital, thus helping to depopulate overcrowded establishments, but they allow the mental patient to receive the support of his kin, and maintain contact with his peers and his world. He will no longer return from 15 years on back wards, like some unkempt and savage Rip van Winkle, a human out of touch with humanity. As research programs in laboratory, clinic, and demonstration projects have clearly emphasized, many of the deteriorating attributes of mental illness can be prevented by drugs and ancillary help in the community, for normal behavior requires the many skills of social living, and these skills are either undeveloped or impaired by hospital isolation.

COMMUNITY MENTAL HEALTH CENTERS

Federal and local resources are now joined in a nationwide effort to prevent incipient psychiatric illness and provide early treatment when it occurs. The approach is inevitably founded on the community. Community Mental Health Centers will be heavily used by schizophrenic patients, and there is every reason to expect that schizophrenia and other disorders will be significantly altered by the program. Many new community centers will establish emergency and consultation services, available to individuals in early stages of difficulty. They will provide diverse out-patient and in-patient treatments for people overtly distressed; and rehabilitation services for patients in remission. To date 125 centers have been funded, although only 25 have received funds for construction and staffing. This program is bound to have important results. It is indeed an extension of improvement already available through pharmacology, community services, and creative uses of non-professional people, an ultimate application of the long and varied researches on mental illness and its treatment.

SUMMARY

This report summarizes current activities of the National Institute of Mental Health in the understanding and solution of problems of schizophrenia. The studies cited here are illustrative of the program and not an exhaustive representation.

In recent years there have been real achievements in the diagnosis, treatment, and rehabilitation of large numbers of people afflicted with schizophrenia. Pharmacology has played an important part in returning the afflicted to some degree of functioning within their communities. New concepts of treatment, and the use of ancillary personnel and community institutions are improving the condition and hopes of those who formerly became backward patients, with many symptoms that were the secondary result of their isolation and poor living conditions. The decline of hospitalized schizophrenics, however, does not reflect a decline in the incidence of illness, for new admissions to hospitals have not been diminishing. Indeed, the rising incidence of childhood schizophrenia represents a major challenge, since failure may mean a crippled life.

The interactive roles of sociocultural factors, of family pathology, and personality variants make this complex illness appear in a baffling diversity of forms. An international collaborative program developed by NIMH with the World Health Organization is hoped to elucidate the critical diagnostic features common to all patients and special to no culture. Improved diagnoses may reveal whether the so-called borderline state is a transient kind of schizophrenia arising under the impact of modern social conditions, milder form of the illness, or something quite apart.

Despite our advances in the study of specific schizophrenic phenomena, the ultimate and important question remains unanswered. The causes of schizophrenia remain a mystery. Athough most of the studies described here are specifically related to schizophrenia, it must be stated emphatically that the eventual understanding of this complex disorder requires an accumulation of knowledge regarding fundamental mechanisms in brain and behavior. The

pathogenesis of schizophrenia involves complex interrelationships within the nervous system, various other body systems, metabolisms, and indeed the interrelationships of individual persons. These can be understood only through fundamental information arising in a variety of sciences.

Basic research on normal thought processes is critical to understanding abnormal thinking. Fundamental knowledge of normal metabolism and brain biochemistry is essential to an understanding of defective mechanisms in an illness such as schizophrenia. Thus, in the final analysis, the contributions that ultimately enable an understanding of schizophrenia will derive from basic research, work that is actually research in schizophrenia although at the time it might not be designated as such by the scientists involved or by those who review their efforts.

Despite the amount of current research, there can be no assurance that the best scientific minds can unfold a solution within a year or two. However, an increasing complement of competent researchers have been attracted to work on a number of new observations that may have considerable significance in leading toward our future understanding of this strange and severe mental illness.

DIRECT RESEARCH

Mr. FLOOD. You are requesting $2,489,000 and seven positions for direct research. Would you comment on the need for this increase?

Dr. YOLLES. The request for the seven positions in this case is for intramural research, for our own direct research activities. Our intramural research activities, direct research activities constitute one of the principal centers of excellence in research in mental health in the United States, in fact, in the world. The NIMH direct research laboratories are considered, if you will, the mecca for mental health research in the United States.

One of the outstanding subject areas of research at the NIMH over the years has been the relationship between the brain and behavior. Some of the most outstanding results, findings in research, have come out of this. The increase that we are talking about at the moment is to set up a brain and behavior laboratory at the experimental farm that NIH operates out at Poolesville. For the first time we now will be able to have free-ranging animals and study some of their reactions. This is a continuation of our brain and behavior research program. The request is for technicians and I believe two professionals, to expand that program.

SPECIAL MENTAL HEALTH PROGRAMS

Mr. FLOOD. There is an increase of $953,000 and 12 positions for what you call special mental health programs.

What are these and why the extra $1 million?

Dr. YOLLES. The special mental health programs include those specialized areas of mental health problems and involve the activities of the Center for Studies of Narcotics and Drug Abuse, the Center for the Prevention and Control of Alcoholism, the Suicide Prevention Center, the Center for Crime and Delinquency, the Center for Studies of Children and Youth as well as the Laboratory of Intermural Training.

The increases we are speaking to here provide first, in the area of the Center for Narcotics and Drug Abuse, four persons and $46,379 to expand the activities of that Center, primarily to expand the number of personnel. They are vastly understaffed.

NATIONAL CENTER FOR PREVENTION AND CONTROL OF ALCOHOLISM

Second, there are four positions for the National Center for Prevention and Control of Alcoholism which administers a support program of research grants, training grants, and demonstration grants, and is running its own intramural research program at St. Elizabeths Hospital at the present time.

Mr. FLOOD. They are going from $5,052,000 to $5,663,000 at the Alcoholism Center.

SUICIDE CENTER

Dr. YOLLES. Yes, sir. The request for the Suicide Center is for two positions and $35,000 to provide two professionals to expand the staff there which is fairly small. They have a total of 10 persons at the present time.

COMMUNITY MENTAL HEALTH RESOURCE SUPPORT

Mr. FLOOD. Under the appropriation heading "Community mental health resource support" you are asking $100,168,000, compared with the adjusted appropriation of $82,081,000 for 1967, but you have an unobligated balance of $43,092,000 that is carried forward from 1966 to 1967. So you will actually have $125,173,000 that is available to you this year. Now you are asking $100,168,000. That is a decrease of $25,005,000.

Dr. YOLLES. It is a statistical artifact.

Mr. FLOOD. A statistical what?

Dr. YOLLES. A statistical artifact of budgeting. The $43,092,000 which you refer to is a carryover of the 2-year funds available from the 1966 appropriation.

UNOBLIGATED BALANCE

Mr. FLOOD. All I want to know is how do you account for this large unobligated balance?

Dr. YOLLES. The funds remain available for 2 years. In the orginal act, the Community Mental Health Center Act, these funds were made available on a 2-year basis because we had predicted that the States must know that the money was available to them. It takes some time then for them to find the matching moneys before applying for a grant. If the moneys were not available for allocation they would be reluctant to go ahead and to seek sources of support. For this purpose we asked for 2-year availability of the money.

Mr. KELLY. This is typical of the pattern on the hospital construction program, too, that we initiated the first year and obligate and start construction in the second year.

Mr. FLOOD. That is a carryover. What did you get in 1966? About $50 million?

Dr. YOLLES. $50 million, yes.

AUTHORIZING LEGISLATION

Mr. FLOOD. Now the $50 million for 1968 for the construction of these community mental health centers is not authorized. What is the status of the authorization?

Dr. YOLLES. The hearings have been held in the House.

Mr. FLOOD. Where is the House bill at this time? Do you know?

Mr. KELLY. They are expecting to hold executive sessions soon to mark up the bill. We learned that last Friday.

APPROVED STATE PLANS

Mr. FLOOD. Are there any States that do not have an approved State plan under the community mental health program?

Dr. YOLLES. There is one State that does not have an approved plan at the present time. That is Montana. We expect that it will be approved before the close of the year.

NARCOTIC ADDICT REHABILITATION FACILITIES

Mr. FLOOD. Now, the last part of this request is brand new; $4 million for construction and operation of narcotic addict rehabilitation facilities. Who is eligible? What kind of facilities will these be? Will there be any matching? What is the story?

Dr. YOLLES. Section 402 of the Narcotic Addict Rehabilitation Act was enacted in the late days of the last session of the Congress and was added to the administration's bill which did not have an authorization for support of community facilities for either construction or operating support of such facilities.

Mr. FLOOD. Rehabilitation facilities, you call them?

Dr. YOLLES. Rehabilitation or treatment facilities for addicts. In the closing days of the session the word "construction" was inserted into section 402 without any further clarification. Funds are therefore available to any agency, public or private, who applies—who has an addiction problem. The restriction on this is that the Surgeon General is authorized to make surveys of the need and to distribute facilities on the basis of such needs. Again a quasi-formula grant distribution will be developed based on the need for narcotic addict rehabilitation facilities in the States.

The $4 million covers not only construction but operation and staffing of such centers.

Mr. FLOOD. Mr. Smith.

LSD

Mr. SMITH. You mentioned LSD a number of times and, of course, many of your research projects involve the use of LSD in therapeutic situations but I notice in your report that you have one project where students were used who had not previously been exposed to LSD and some of them were given a high-level dosage and others a lower dosage. Do you think that it is proper to use LSD in research in a nontherapeutic situation?

Dr. YOLLES. I believe that was done some time ago and it would be looked at from a different point of view at the present time. As a matter of fact, the results of this study do not indicate any significant effects on the individual.

Mr. SMITH. It was in a recent report, however, was it not?

Dr. YOLLES. It was just reported recently but the work was done some time ago, yes.

Dr. YOLLES. It was reported in terms of looking back and assessing the effects of LSD on individuals. In terms of long-range effects of LSD we really know very little. Similarly with marijuana. We are

trying to collect as many previous studies as we can to see what long-term effects the drugs really have.

Mr. SMITH. How habit forming are these two drugs?

Dr. YOLLES. LSD is not habit forming in the usual sense of being addictive; neither is marijuana. There is a psychological disposition toward using it again, but it is not a real physical addiction in which you have withdrawal signs if the drug is discontinued.

TELEVISION AND MENTAL HEALTH

Mr. SMITH. In your presentation you did mention that 14-year-olds and 12- and 13-year-olds are having mental health problems out of proportion to their numbers in the population, but nothing was mentioned about television. Do certain kinds of programs contribute to mental problems for this age child?

Dr. YOLLES. I wish I could answer that for you very directly.

Mr. SMITH. Have you tried to secure answers to it?

Dr. YOLLES. Yes, we have been trying to for a number of years through a number of research studies. The results in some studies are diametrically opposed, in others they are equivocal. A great deal more work has to be done in this area. It is related to another area which has not been under active research but which we hope to develop and that is the area of pornography—obscenity and its effect on mental health. There are two schools of thought. Those who will say it has very dire effects on the individual and others who say it has no effect. The same thing is true of television, we don't quite know what effects scenes of violence on television, for example, have on the mental health of the child.

PHYSICAL THERAPY IN TREATMENT OF MENTAL PATIENTS

Mr. SMITH. What about physical therapy in the treatment of mental patients? I notice in some States they are disposing of their farm setup in connection with mental institutions. It used to be they thought that if some patients were able to be out of doors, and they were permitted to exercise in an interesting way, it was good therapy.

Dr. YOLLES. Well, you are quite right, the trend is changing. In the 1920's it was believed that so long as you provided fresh air and sunlight it would cure everything, including mental illness. We now know differently.

For example, in the treatment of narcotic addicts it was also proposed that this be done and, in effect, it was done. In fact, the original name of our institution at Lexington was the First U.S. Narcotic Farm. The reasoning was the same. But to take an individual from the Lower East Side of New York and have him attending cows as occupational therapy, hardly seems to the point today. It has taken us a number of years but we are getting away from that now. Most State hospitals are doing away with their farms.

Mr. SMITH. They think there is no patient, then, that would be benefited by this type of therapy?

Dr. YOLLES. I suspect there are some who would, as an occupational therapy, be improved by working on a farm if this is their disposition, their predisposition. But as a vast investment for a mental health

facility in terms of treatment I do not think it pays for itself. There are other occupational therapies which are, we feel, capable of producing a higher yield.

EFFECT OF SEPARATION FROM NIH

Mr. SMITH. Your shop has been separated from NIH for a year. What have been the benefits and what have been the losses as a result?

Dr. YOLLES. No, sir, not quite a year. Since January 1.

Mr. SMITH. What can you see in this length of time as benefits compared to losses?

Dr. YOLLES. Generally speaking, one of the benefits is having a focal point at the bureau level in the PHS. It is the recognition of the importance of the problem of mental health in the United States.

Mr. SMITH. You mean, you were smothered under the other illnesses when you were under NIH?

Dr. YOLLES. Not so much we were smothered but it is a recognition that one of the largest problems in the United States today is mental illness and that it is, in a sense, on a par with the totality of other ilnesses. There are over 100 mental and emotional illnesses which we combine under the one title of "mental illness." The recognition of the importance of this national problem by elevation of the National Institute of Mental Health to the status of one of the five bureaus of the Public Health Service has meant much to mental health professionals out in the field. It is a recognition, public recognition, of the importance of the program. It is a little early to really be able to give you any answers about any difficulties we have had.

Mr. KELLY. I think you should understand that in the context of NIH, the National Institute of Mental Health was always somewhat of an oddity because a substantial part of its program is other than research. It has a program for service training and it has a program of support of community programs and the construction of community facilities and State-controlled programs and assistance to State mental hospitals. None of the other NIH Institutes carry out such training and service programs.

Mr. SMITH. Now, you are proposing an increasing number of research projects, are you not, with regard to drugs and other things?

Dr. YOLLES. We intend to expand this area of drug research. For example, the area which has come into prominence in the last few days, the area of treatment of manic depressive psychosis with a common chemical substance called lithium carbonate.

Mr. SMITH. Will you be able to coordinate your research activities and operate as efficiently under this organizational structure as you could have under the other?

Dr. YOLLES. I would hope so. We have every hope of doing so and we have been working closely with NIH because of common ties and we hope to continue to do that.

Mr. SMITH. That is all I have, Mr. Chairman.

Mr. FLOOD. Mr. Casey.

FIELD STATIONS

Mr. CASEY. Thank you, Mr. Chairman.

Doctor, have you established the location for your field stations yet?

Dr. YOLLES. No, sir; we have not. Some may view this as procrastination but we have been looking toward the establishment of field stations for a long, long time. This represents to us the culmination of a great deal of effort in terms of setting out field stations. We hope to have about six to eight of them which will test the climate of the country, so to speak, as far as mental health is concerned. We are looking very, very carefully and very, very cautiously around the United States to find the best place to set these field stations. The exact locus for the first field station is still under consideration.

Mr. CASEY. The reason I ask is, of course, the State Psychiatric Institute at Houston is very interested in being inspected and evaluated. They think they have something to offer there. Of course, they would like very much to have your field station down there. I just wondered if you had made any choices yet or any selections. How long do you think it will be before you will make such selections?

Dr. YOLLES. Our staff are going out and doing intensive visiting and consultation with all possible applicants and it is a little difficult for me to say at this point as to when.

STAFFING GRANTS

Mr. CASEY. Now I notice on your chart you have on the staffing grants, it looks like maybe 15, 20 percent funded and the rest are pending. Is that correct?

Dr. YOLLES. This is as of February.

Mr. CASEY. For 1967?

Dr. YOLLES. Yes, sir.

Mr. CASEY. And you have——

Dr. YOLLES. But we actually have applications in-house in the regional offices. The pending category includes applications in hand that have not been approved as yet.

Mr. CASEY. How long does it take you to process an application for a staffing grant?

Dr. YOLLES. Depending on the time of the year, on the press of circumstances it takes about 2 months from the time the individual has his application prepared to having it actually approved. The actual approval of these grants is done by the regional health director. They come to the National Institute of Mental Health for central review and then go back and are approved there.

HEDGECROFT HOSPITAL IN HOUSTON

Mr. CASEY. Did Hedgecroft Hospital at Houston ever get an approvable program?

Dr. YOLLES. I believe it received both a staffing and a construction grant.

Mr. CASEY. Have you announced that? Do they know they have it?

Dr. YOLLES. I guess I was incorrect on that one. It is still in the house.

Mr. CASEY. It has not been approved?

Dr. YOLLES. No. There is one pending. It is still pending in the Institute.

Mr. CASEY. How long has that one been pending now?

Dr. YOLLES. I really could not tell you. I would have to check. I do not have the record here.

Mr. CASEY. About a year, isn't it?

Dr. YOLLES. I really do not know. I understand there was some difficulty with the application in terms of resubmitting it and modifying it but I do not know what the exact status is.

Mr. CASEY. I think you have some correspondence from me on that. I would like to know what the status of it is. If they cannot qualify I think you ought to tell them and tell me and let's get rid of it one way or the other.

COMMUNITY MENTAL HEALTH CENTERS

How many community mental health centers do you think you can take care of with the moneys you are asking for? That is, in the way of staffing and construction grants? Is this construction?

Dr. YOLLES. That is the total numbers funded because there is an overlap in many cases between ones that receive a staffing grant and the ones that receive a construction grant.

Mr. CASEY. When you fund them and give them a staffing grant is that for just 1 year or a period of years, or what?

Dr. YOLLES. No, sir; it is a grant for a period of 4 years and 3 months, and it is on a gradually declining matching basis, starting with 75 percent of the initial costs of staffing the first 15 months and then 60 percent in the following year after the first 15 months, and then 45 percent, then 30 percent, and then the Federal share is discontinued.

Mr. CASEY. The idea is that they are supposed to get on their own feet?

Dr. YOLLES. Yes, sir.

Mr. CASEY. This is to get them off the ground and prove their worth to the community?

Dr. YOLLES. Exactly.

Mr. CASEY. Whether it is a nonprofit organization or a State or local government operation?

Dr. YOLLES. Yes. We have seen a good deal of difficulty where a community has attempted to construct a facility and had to find the matching money to do so. When the facility is completed it finds it has exhausted its supplies of local funding. The community is then unable, really, to staff and to open as much of the facility as they thought they would like to. This program was deliberately designed to help communities to start their services right now when they are in need and gradually develop their local sources of support over 4 years and 3 months.

LITHIUM CARBONATE

Mr. CASEY. Lithium carbonate you say is very common or simple?

Dr. YOLLES. It is a very common chemical substance which is used for the glaze on pottery.

Some 15 years ago in Australia a gentleman working with animals and animal behavior found that it reduced the excitement in animals and they experimented with the drug from time to time both here and on the continent in Europe.

They found that it has a very remarkable effect on the manic phase of manic depressive psychosis. The "high" phase, when the person is really excited. As a matter of fact, it really is the most effective drug

for this condition that we have today and is effective in somewhere between 60 to 85 percent of all cases versus something like 55 percent for the best tranquilizer used. Even more startling than that—and this is a startling fact in itself—it is the first drug which is available to us which will prevent the recurrence of a major psychosis. In one series of 88 cases that we know, Danish investigators with whom we have been collaborating have found that lithium increased the period between recurrences from an average time period of 8 months to somewhere between 5 and 7 years. This has been a remarkable achievement. The drug also offers us an unusual means of studying brain chemistry. It allows us to study some of the special substances in the brain which affect depression and elation as well as some of the other mental disorders.

So it has been, all and all, a very useful drug but it has been hidden somewhere for 15 years.

Mr. CASEY. Do you still use thorazine?

Dr. YOLLES. Yes, sir; and quite effectively in emotional disturbances. But for this specific type of illness, lithium carbonate is much more effective.

Mr. CASEY. I believe that is all.

Mr. FLOOD. Well, you had quite a workout and you did very well. It was an excellent presentation.

Dr. YOLLES. Thank you, sir.

JUSTIFICATION MATERIAL

Mental Health Research and Services

Amounts available for obligation

	1967	1968
Appropriation	$264, 119, 000	$246, 741, 000
Transfer to "Operating expenses, Public Buildings Service," General Services Administration	−515, 000	
Comparative transfer to—		
"Community health services"	−8, 972, 000	
"Community mental health resource support"	−32, 081, 000	
"Comprehensive health planning and services"	−6, 750, 000	
Comparative transfer from "Hospitals and medical care"	[1] 9, 246, 000	
Advances and reimbursements from—		
Other accounts	[2] 323, 000	1, 727, 000
Non-Federal sources	4, 000	4, 000
Proposed for separate transmittal	2, 000, 000	
Total	227, 374, 000	248, 472, 000

[1] Includes reimbursements of $1,400,000 in 1967.
[2] Excludes comparatively transferred reimbursements of $1,400,000 in 1967, which are included under comparative transfer from "Hospitals and medical care," above.

Obligations by activities

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research		$71, 631, 000		$76, 477, 000		$4, 846, 000
(General research support)		(6, 434, 000)		(5, 667, 000)		(−767, 000)
(Scientific evaluation)		(274, 000)		(375, 000)		(100, 000)
(Categorical clincial research centers)		(1, 750, 000)		(1, 750, 000)		
Hospital improvement		10, 610, 000		10, 610, 000		
Training		92, 266, 000		100, 762, 000		8, 496, 000
Fellowships		9, 133, 000		9, 859, 000		726, 000
Direct operations:						
Planning, development and administration of extramural research programs	112	2, 473, 000	114	2, 550, 000	2	77, 000
Intramural research	519	13, 625, 000	526	16, 114, 000	7	2, 489, 000
Manpower and training	87	1, 653, 000	87	1, 703, 000		50, 000
Mental health services	81	1, 554, 000	81	1, 550, 000		−4, 000
Special mental health programs	147	2, 287, 000	159	3, 240, 000	12	953, 000
Regional and field activities	283	4, 648, 000	321	7, 588, 000	38	2, 940, 000
Fort Worth and Lexington hospitals	1, 072	10, 967, 000	1, 072	10, 540, 000		−427, 000
Scientific communication and public education	73	1, 640, 000	73	2, 640, 000		1, 000, 000
Program management and services	323	4, 731, 000	325	4, 839, 000	2	108, 000
Total obligations	2, 697	227, 218, 000	2, 758	248, 472, 000	61	21, 254, 000
Unobligated balance, reserve		156, 000				−156, 000
Total, obligations and balance	2, 697	227, 374, 000	2, 758	248, 472, 000	61	21, 098, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
PUBLIC HEALTH SERVICE			
Total number of permanent positions	2,683	2,744	+61
Full-time equivalent of all other positions	194	194	
Average number of all employees	2,505	2,666	+161
11 Personnel compensation:			
Permanent positions	$19,745,000	$21,201,000	+$1,456,000
Positions other than permanent	1,177,000	1,177,000	
Other personnel compensation	427,000	427,000	
Total personnel compensation	21,349,000	22,805,000	+1,456,000
12 Personnel benefits	2,154,000	2,251,000	+97,000
21 Travel and transportation of persons	1,308,000	1,355,000	+47,000
22 Transportation of things	276,000	183,000	−93,000
23 Rent, communications, and utilities	997,000	1,115,000	+118,000
24 Printing and reproduction	250,000	253,000	+3,000
25 Other services	7,137,000	11,901,000	+4,764,000
Payment to "National Institutes of Health management fund"	6,284,000	6,926,000	+642,000
26 Supplies and materials	2,169,000	2,092,000	−77,000
31 Equipment	1,503,000	1,754,000	+251,000
41 Grants, subsidies and contributions	183,682,000	197,728,000	+14,046,000
Subtotal	227,109,000	248,363,000	+21,254,000
95 Quarters and subsistence charges	−29,000	−29,000	
Total, Public Health Service	227,080,000	248,334,000	+21,254,000
ALLOCATION TO ST. ELIZABETHS HOSPITAL			
Total number of permanent positions	14	14	
Average number of all employees	14	14	
11 Personnel compensation:			
Permanent positions	$88,000	$88,000	
Other personnel compensation	15,000	15,000	
Total personnel compensation	103,000	103,000	
12 Personnel benefits	8,000	8,000	
23 Rent, communications, and utilities	24,000	24,000	
25 Other services	1,000	1,000	
26 Supplies and materials	2,000	2,000	
Total, St. Elizabeths Hospital	138,000	138,000	
Total, obligations by object	227,218,000	248,472,000	+21,254,000

Summary of changes

1967 enacted appropriation	$264,119,000
Transfer to "Operating expenses, Public Buildings Service," General Services Administration (space rental)	−515,000
Comparative transfer to:	
"Community health services"	−8,972,000
"Community mental health resource support"	−32,081,000
"Comprehensive health planning and services"	−6,750,000
Comparative transfer from: "Hospitals and medical care"	[1] 9,246,000
1967 estimated reimbursements	[1] 327,000
Proposed supplemental	2,000,000
Unobligated balance, reserve	−156,000
1967 total estimated obligations	227,218,000
1968 appropriation estimate	246,741,000
1968 estimated reimbursements	1,731,000
1968 estimated obligations	248,472,000
Total change	+21,254,000

[1] $1,400,000 of the comparative transfer from "Hospitals and medical care" is reimbursements.

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
A. Built in: 1. Annualization of positions new in 1967				$1,256,000
B. Program:				
1. Research grants		$62,947,000		6,113,000
(a) Regular projects		(62,672,000)		(5,509,000)
(b) Surveys and demonstrations, Narcotic Addict Rehabilitation Act				(504,000)
(c) Scientific evaluation		(275,000)		(100,000)
2. Training		92,266,000		8,496,000
3. Fellowships		9,133,000		726,000
4. Planning, development, and administration of extramural research programs	112	2,473,000	2	83,000
5. Intramural research	519	13,625,000	7	1,860,000
6. Manpower and training	87	1,653,000		50,000
7. Special mental health programs	147	2,287,000	12	957,000
8. Regional and field activities	283	4,648,000	38	1,763,000
9. Scientific communication and publication	73	1,640,000		1,000,000
10. Program management and services	323	4,731,000	2	112,000
Subtotal program increases			61	21,160,000
Payment to National Institutes of Health management fund for centrally furnished services		6,284,000		642,000
Total program increases			61	21,802,000
Total increase				23,058,000
DECREASES				
A. Nonrecurring other objects				−502,000
B. 1 less day of pay in 1968 (261 days in 1967, 260 days in 1968)				−35,000
C. Program:				
1. General research support grants		6,434,000		−767,000
2. Study of children's emotional illnesses		500,000		−500,000
Subtotal program decreases				−1,267,000
Total decreases				−1,804,000
Total net changes requested			+61	+21,254,000

Explanation of Changes

Research Grants.—The increase of $5,509,000 will provide for additional grants in the areas of behavioral sciences; clinical research; psychopharmacology research; narcotic and drug abuse; alcoholism; metropolitan mental health problems; and suicide prevention. An increase of $504,000 will support project grants under the provisions of the Narcotic Addict Rehabilitation Act of 1966. An increase of $100,000 for scientific evaluation grants is also provided. These increases are offset by a decrease of $767,000 in the general research support program and $500,000 in the study of children's emotional illnesses.

Training Grants.—An increase of $8,496,000 will provide for 13 new grants and $500,000 in undergraduate training, 96 grants and $5,252,000 in the graduate program; 31 grants and $1,150,000 for continuing education; 17 grants and $1,000,000 for experimental and special training; and 30 grants and $550,000 for the inservice training program. The remaining $44,000 is for an additional scientific evaluation grant.

Fellowships.—The $726,000 increase will support 116 additional grants in the predoctoral program and 5 new grants in the research career development program.

Planning, Development and Administration of Extramural Research Programs.—Two positions and $83,000 will be used to strengthen the grants review activities of the extramural research program.

Intramural Research.—The 7 positions and $1,860,000 increase will provide: $500,000 for renovating Clinical Center space for psychiatric research; $450,000 for additional data processing and computer facilities; $210,000 for equipment for expansion of the laboratory of neurochemistry. The 7 positions and the

remaining $700,000 will provide for additional staff in animal behavior studies relating to learning, problem solving, etc.; also studies of the metabolism of addicting drugs in man and field follow-up studies of former drug patients.

Manpower and Training.—The additional $50,000 will be used to support studies of mental health manpower needs.

Special Mental Health Programs.—The increase of 12 positions and $957,000 will provide for additional staff, data processing, and other contractual services in support of the centers on narcotic and drug abuse, alcoholism, crime and delinquency, suicide prevention, and mental health of children and youth.

Regional and Field Activities.—The increase of 38 positions and $2,944,000 provides 36 positions and $2,849,000 to carry out the Institute's responsibilities under the Narcotic Addict Rehabilitation Act, and 2 positions and $95,000 to strengthen staff functions of the overall regional and field program.

Fort Worth and Lexington Hospitals.—The decrease of $427,000 in this activity includes $353,000 for nonrecurring other objects costs related to the establishment of the programs under the Narcotic Addict Rehabilitation Act of 1966. Also included is a reduction of $74,000 for nonrecurring equipment costs in the on-going programs.

Scientific Communication and Public Education.—An increase of $1,000,000 will be utilized for the development of a scientific and public information program on narcotics and dangerous drugs.

Program Management and Services.—Two positions and $112,000 will provide staff and supporting funds in the grants and contracts management section.

Included in the overall change is an increase of $75,000 for annualization of positions new in 1967, offset by a decrease in the same amount in nonrecurring equipment, also a decrease of $35,000 for one less day of pay in 1968.

Authorizing Legislation for Grants

I. The following Sections of the Public Health Service Act authorize grants made under the subactivities "Research," "Hospital Improvement," "Training," and "Fellowships."

"Sec. 301. The language of this Section will be found under the tab "Preamble Paragraph" in Volume V.

"Sec. 302. (a) In carrying out the purposes of Section 301 with respect to narcotics, the studies and investigations shall include the use and misuse of narcotic drugs, the quantities of crude opium, coca leaves, and their salts, derivatives, and preparations, together with reserves thereof, necessary to supply the normal and emergency medicinal and scientific requirements of the United States. The results of studies and investigations of the quantities of crude opium, coca leaves, or other narcotic drugs, together with such reserves thereof, as are necessary to supply the normal and emergency medicinal and scientific requirements of the United States, shall be reported not later than the 1st day of September each year to the Secretary of the Treasury, to be used at his discretion in determining the amounts of crude opium and coca leaves to be imported under the Narcotic Drugs Import and Export Act, as amended.

"(b) The Surgeon General shall cooperate with States for the purpose of aiding them to solve their narcotic drug problems and shall give authorized representatives of the States the benefit of his experience in the care, treatment, and rehabilitation of narcotic addicts to the end that each State may be encouraged to provide adequate facilities and methods for the care and treatment of its narcotic addicts.

"Sec. 303. (a) In carrying out the purposes of section 301 with respect to mental health, the Surgeon General is authorized—

"(1) to provide training and instruction and to establish and maintain traineeships, in accordance with the provisions of section 433 (a);

"(2) to make grants to State or local agencies, laboratories, and other public or nonprofit agencies and institutions, and to individuals for investigations, experiments, demonstrations, studies, and research projects with respect to the development of improved methods of diagnosing mental illness, and of care, treatment, and rehabilitation of the mentally ill, including grants to State agencies responsible for administration of State institutions for care, or care and treatment, of mentally ill persons for developing and establishing improved methods of operation and administration of such institutions.

"(b) Grants under paragraph (2) of subsection (a) may be made only upon recommendation of the National Advisory Mental Health Council. Such grants

may be paid in advance or by way of reimbursement, as may be determined by the Surgeon General; and shall be made on such conditions as the Surgeon General finds necessary."

II. The following Section of the Narcotic Addict Rehabilitation Act of 1966 authorizes grants under the subactivity "Research":

"SEC. 402. (a) (1) to make grants to States and political subdivisions thereof and to private organizations and institutions (A) for the development of field testing and demonstration programs for the treatment of narcotic addiction, . . ."

Explanation of transfers

	1967 estimate	Purpose
Transferred to: "Operating expenses, Public Buildings Service," General Services Administration.	−$515,000	Transfer of rental costs.
Comparative transfer from: "Hospitals and medical care."	+9,246,000	Transfer of Fort Worth and Lexington Hospitals, as part of the Public Health Service reorganization.
Comparative transfer to—		
"Community health services"	−8,972,000	Transfer of mental retardation hospital improvement grants as part of the Public Health Service reorganization.
"Community mental health resource support.	−32,081,000	Transfer of mental health staffing grants program to this new appropriation title.
"Comprehensive health planning and services."	−6,750,000	Transfer of State control (grant-in-aid) program as part of the Public Health Service reorganization.

RESEARCH GRANTS

	1967 estimate	1968 estimate	Increase or decrease
Regular programs	$62,672,000	$68,181,000	+$5,509,000
Special programs	8,959,000	8,296,000	−663,000
Total research grants	71,631,0000	76,477,0000	+4,846,000

The objective of the research grant program of the National Institute of Mental Health (NIMH) is to provide support for research on the etiology, diagnosis, treatment, prevention and control of mental illness, and the promotion of mental health. The Institute is responsible, therefore, for the support of both clinical and basic research aimed either at the resolution of specific problems of mental and emotional illness or at the enlargement of knowledge regarding the parameters of human behavior—including its prediction and control, as well as for support of applied research aimed at applying newly discovered information and techniques. Reflected in the range of research grant activities is a recognition by the Institute that if we are to build a continuum of services to enhance the mental health of Americans, we must buttress the effort with a continuum of scientific endeavor—from basic, normative studies to community based evaluations of new approaches to the care of the severely disturbed.

The research grant program supports research projects in the following areas: behavioral sciences, clinical research, applied research, psychopharmacological research in narcotics and drug abuse, research in alcoholism, metropolitan mental health problems, and research in suicide prevention. This subactivity also includes a proportionate share of support for General Research Support grants which are administered by the Division of Research Facilities and Resources, National Institutes of Health.

Research grants are awarded on an individual project basis. Awards are made after review by non-government scientists organized into "study section" or review committees. Following study section review an application receives a second review, by the National Advisory Mental Health Council, a statutory group made up of mental health scientists and experts and interested citizens. Following its review the Council recommends to the Surgeon General either approval or disapproval of each grant. No grant may be awarded unless it has been recommended by the National Advisory Mental Health Council. The vari-

ous research programs supported by grants are discussed under the appropriate subactivities of direct operations.

Distribution of research grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting projects	1,102	$38,889,000	1,230	$43,112,000	+128	+$4,223,000
2. Competing projects	183	7,686,000	192	8,100,000	+9	+414,000
3. Supplementals	(34)	1,456,000	(42)	1,560,000	(+8)	+104,000
4. New	493	14,641,000	507	15,409,000	+14	+768,000
5. Subtotal, regular programs	1,778	62,672,000	1,929	68,181,000	+151	+5,509,000
6. General research support grants		6,434,000		5,667,000		−767,000
7. Scientific evaluation		275,000		375,000		+100,000
8. Clinical research centers		1,750,000		1,750,000		
9. Research projects under Narcotic Addict Rehabilitation Act				504,000		+504,000
10. Study of children's emotional illnesses		500,000				−500,000
11. Subtotal, special programs		8,959,000		8,296,000		−663,000
12. Total, research grants	1,778	71,631,000	1,929	76,477,000	+151	+4,846,000

Research grants program analysis

Fields	1967 estimate	1968 estimate	Increase or decrease
1. Behavioral sciences	$13,817,000	$15,900,000	+$2,083,000
2. Clinical research	8,211,000	9,233,000	+1,022,000
3. Applied research	20,798,000	20,798,000	
4. Psychopharmacology research	9,616,000	10,300,000	+684,000
5. Narcotics and drug abuse	3,236,000	3,900,000	+664,000
6. Alcoholism	4,288,000	4,500,000	+212,000
7. Metropolitan M. H. problems	371,000	950,000	+579,000
8. Suicide prevention	2,335,000	2,600,000	+265,000
9. Subtotal	62,672,000	68,181,000	+5,509,000
10. General research support grants	6,434,000	5,667,000	−767,000
11. Scientific evaluation	275,000	375,000	+100,000
12. Categorical clinical research centers	1,750,000	1,750,000	
13. Research projects under NARA		504,000	+504,000
14. Study of children's emotional illnesses	500,000		−500,000
15. Subtotal, special programs	8,959,000	8,296,000	−663,000
16. Total research grants	71,631,000	76,477,000	+4,846,000

Hospital Improvement Grants

Hospital improvement grants:

1967 estimate	$10,610,000
1968 estimate	10,610,000
Increase or decrease	0

The purpose of the Hospital Improvement Project program is to provide support for demonstrations of improved methods of care, treatment, and rehabilitation of the mentally ill in state mental hospitals. Its objectives are to strengthen therapeutic services and improve the quality of patient care, and to increase the contributions that these institutions can make as an integral part of the comprehensive community mental health programs of the future. This program is discussed in greater detail under mental health services.

In 1967, 97 grants and $6,790,000 hospital improvement projects to institutions for the mentally retarded were transferred to the Community Health Services program of the Bureau of Health Services.

Distribution of hospital improvement grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	86	$7,642,000	122	$10,610,000	+36	+$2,968,000
2. Competing continuations and new grants	36	2,968,000			−36	−2,968,000
3. Total	122	10,610,000	122	10,610,000		

Training Grants

Training grants:

1967 estimate	$92,266,000
1968 estimate	100,762,000
Increase or decrease	+8,496,000

The primary objective of the Institute's training program is to increase the number of specialists in the mental health field. To meet this goal, a wide variety of training opportunities are provided for all levels of personnel engaged in mental health work; professional personnel in clinical service, research, training, and administration; sub-professional and technical personnel—including those receiving inservice training in institutions for the mentally ill; and general practitioners and other non-psychiatric specialists prepared to assume a more effective role in psychiatric treatment. Training is also provided in such special areas as alcoholism, suicide prevention, metropolitan mental health problems, drug abuse and narcotics, and support is provided for pilot projects to develop new and imaginative programs of training in mental health skills.

Training efforts are directed at providing—by 1970—over 87,000 trained mental health personnel in the four core mental health disciplines of pyschiatry, psychology, social work and nursing. The Institute's training program will provide crucial manpower support in behalf of the Nation's community mental health program. Other National programs, e.g., Medicare and Headstart, will increasingly utilize the skills of mental health personnel. The necessity of pursuing a well coordinated and productive training effort is, therefore, clear.

These programs are discussed in detail under the subactivity Manpower and training.

In 1967, 99 grants and $2,182,000 in inservice training grants to institutions for the mentally retarded were transferred to the Community Health Services program of the Bureau of Health Services.

Distribution of training grants

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
a. Noncompeting	1,335	$63,045,000	1,639	$74,626,000	+304	+$11,581,000
b. Competing	365	16,717,000	358	16,856,000	−7	+139,000
2. Supplementals	(308)	2,409,000	(307)	1,323,000	(−1)	−1,086,000
3. New	323	9,945,000	213	7,763,000	−110	−2,182,000
4. Scientific evaluation	(2)	150,000	(3)	194,000	(+1)	+44,000
5. Total training grants	2,023	92,266,000	2,210	100,762,000	+187	+8,496,000

Summary

Training grants (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Undergraduate	294	$8,500,000	307	$9,000,000	+13	+$500,000
2. Graduate	1,296	70,348,000	1,392	75,600,000	+96	+5,252,000
3. Continuing education	121	2,800,000	152	3,950,000	+31	+1,150,000
4. Experimental and special	113	5,800,000	130	6,800,000	+17	+1,000,000
5. Inservice	199	4,668,000	229	5,218,000	+30	+550,000
6. Scientific evaluation	(2)	150,000	(3)	194,000	(+1)	+44,000
7. Total training grants	2,023	92,266,000	2,210	100,762,000	+187	+8,496,000

Training grants program analysis

Disciplines	1967 estimate	1968 estimate	Increase or decrease
Psychiatry	$27,730,000	$29,080,000	+$1,350,000
Behavioral sciences	18,000,000	19,750,000	+1,750,000
Psychiatric nursing	10,300,000	10,900,000	+600,000
Social work	12,300,000	12,900,000	+600,000
Narcotics and drug abuse	137,000	231,000	+94,000
Alcoholism	256,000	430,000	+174,000
Metropolitan mental health problems	25,000	40,000	+15,000
Suicide prevention	250,000	422,000	+172,000
General practitioner	9,850,000	10,250,000	+400,000
Experimental and special	5,800,000	7,397,000	+1,597,000
Continuing education	2,800,000	3,950,000	+1,150,000
Inservice training	4,668,000	5,218,000	+550,000
Scientific evaluation	150,000	194,000	+44,000
Total	92,266,000	100,762,000	+8,496,000

Training grants program analysis

	Estimate, 1967			Estimate, 1968			Increase or decrease		
	Number of—		Amount	Number of—		Amount	Number of—		Amount
	Grants	Stipends		Grants	Stipends		Grants	Stipends	
Undergraduate	294	1,766	$8,500,000	307	1,835	$9,000,000	+13	+69	+$500,000
Graduate	1,296	8,335	70,348,000	1,392	9,032	75,600,000	+96	+697	+5,252,000
Research training	(207)	(1,356)	(10,500,000)	(233)	(1,568)	(12,200,000)	(+26)	(+212)	(+1,700,000)
General practitioner	(257)	(665)	(9,850,000)	(268)	(682)	(10,250,000)	(+11)	(+17)	(+400,000)
All other	(832)	(6,314)	(49,998,000)	(891)	(6,782)	(53,150,000)	(+59)	(+468)	(+3,152,000)
Continuing education	121	75	2,800,000	152	125	3,950,000	+31	+50	+1,150,000
Experimental and special	113	958	5,800,000	130	1,005	6,800,000	+17	+47	+1,000,000
Inservice training	199	.....	4,668,000	229	.....	5,218,000	+30	.....	+550,000
Scientific evaluation	(2)	.....	150,000	(3)	.....	194,000	(+1)	.....	+44,000
Total	2,023	11,134	92,266,000	2,210	11,997	100,762,000	+187	+863	+8,496,000

Fellowships

Fellowships:	
1967 estimate	$9,133,000
1968 estimate	9,859,000
Increase or decrease	+726,000

Fellowships programs provide support for scientists engaged in research on the problems of mental health and mental illness. Programs range from those which support young investigators beginning careers in the biomedical and behavioral sciences relevant to mental health, to those that support fully qualified research scientists in positions favorable to the development of research careers.

These programs are discussed in detail under the appropriate subactivities of Direct Operations.

Distribution of fellowships

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Continuations:						
(a) Noncompeting	498	$4,882,900	569	$5,592,000	+71	+$710,000
(b) Competing	73	876,000	133	1,080,000	+60	+204,000
2. New	474	3,375,000	464	3,187,000	−10	−188,000
3. Total fellowships	1,045	9,133,000	1,166	9,859,000	+121	+726,000

Fellowships (by type of program)

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Predoctoral	730	$3,933,000	844	$4,560,000	+114	+$627,000
2. Postdoctoral	74	490,000	75	495,000	+1	+5,000
3. Special	79	920,000	80	960,000	+1	+40,000
4. Research career:						
a. Career	25	716,000	25	720,000	0	+4,000
b. Development awards	137	3,074,000	142	3,124,000	+5	+50,00
5. Total fellowships	1,045	9,133,000	1,166	9,859,000	+121	+726,000

Planning, Development, and Administration of Extramural Research Programs

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	112	$1,492,000	114	$1,502,000	+2	+$10,000
Other expenses		981,000		1,048,000		+67,000
Total	112	2,473,000	114	2,550,000	+2	+77,000

Major research program

The Institute's extramural research program is build upon a foundation of braadly-based research in the areas of clinical, behavioral, psychopharmacology and applied research. Included is a spectrum of studies concerning causes of the various mental and emotional illnesses; the biological, psychological and social processes associated with these disorders; their incidence and prevalence; and the identification and validation of new and improved methods for their diagnosis, treatment, and control through drugs and other modes of therapy.

A large portion of the Institute's research program is directed at the conquest of the major mental illnesses—the schizophrenias, the depressions, and other

psychotic, neurotic and character disorders. These studies range over the biological, psychological, and social fields—as investigators attempt to learn more not only about specific etiological factors, but also about improved methods of prevention and treatment.

Among many urgent mental health problems, the group of disorders—labelled schizophrenia presents a challenge to society at large, to clinical practice, and to our overall understanding of the psychopathology of human behavior. Many studies are designed to identify unique biological factors which differentiate schizophrenic and normal subjects in order to distinguish and describe differences in their overt behavioral and physiological functioning. Still other scientists have been attempting to determine the incidence of schizophrenia among children whose parents have a history of schizophrenia in order to shed some light on genetic factors of this illness.

More systematic studies of etiology—particularly of genetic and environmental factors and their interaction—will be developed further, along with longitudinal studies to illustrate the course and natural outcome of this illness. Also to be stimulated are more studies of the physiological properties of abnormal chemical substances in various body fluids found to be associated with schizophrenia. A newly developed Center for Studies of Schizophrenia will be devoted to the coordination and development of new research, clinical, and training activities in this critical area.

Although many fundamental and challenging issues remain concerning the biological, biochemical and psychological determinants of the depressions, research efforts directed at treatment have become successively more refined and have achieved a considerable measure of success. For example, there has been an increasing emphasis on studying the comparative effectiveness of several drugs found to be useful in depression. The identification of sleep patterns typical of depressives has offered not only a diagnostic aid, but also an opportunity for more selective drug treatment. An increased number of studies are continuing to shed additional light on the biochemical correlates of depression—catecholamine metabolism, electrolyte balance, and endocrine function.

Many of the Institute's behavioral science studies focus on the relationship between brain and behavior. Knowledge of the mechanisms and processes through which the central nervous system controls and regulates behavior is essential to an eventual understanding of mental and emotional disturbance. Electrophysiological, anatomical and chemical techniques are in use by many investigators reaching for an understanding of the role that areas of the brain play in such phenomena as perception, learning, motivation, and emotion. Studies are in progress to identify neural centers apparently associated with basic human drives including aggressive behavior.

In view of heightened recognition of the need to understand the nature and role of sleep and dreams, new studies in this area have been carried out by an increasing number of investigators. Several major advances have been made in understanding the nature and function of sleep and dreaming in everyday life and in mental illness.

Behavioral scientists continue their efforts to understand the role of psychological, social, and cultural factors in the etiology, course, and treatment of mental illness. We are gaining, for example, a sharper understanding of the importance to the child of early impressions; how attitudes, values and standards develop. We are winning new insights into the complex patterns of family interaction, and how they can give rise to abnormal behavior. We are seeing more clearly some of the psychological and social frustrations that lead to aggressive behavior and delinquency. In addition, we are tracking the psychological factors that help generate physical illnesses. Recent studies suggest that feelings of despair and hopelessness in handling a difficult life situation may be associated with the origin of a wide range of physical diseases.

Next year will see continued support and further development of studies in the behavioral sciences in areas similar to those identified above, as well as in other substantive areas such as behavioral genetics, computer simulation of behavior, language and communication, motivation, problem solving and decision making, and the role of endocrine balance in behavior.

One of the major areas of successful growth in the Institute's program has been in psychopharmacology—both at the level of basic studies and in terms of clinical application. Many advances have been made in the assessment and evaluation of pharmacological properties of new compounds, their general physiological and behavioral effects on animal and human subjects as well as their

clinical efficacy in the treatment of such disorders as the schizophrenias and the depressions. The therapeutic value of many new drugs continues to be assessed in a variety of treatment settings and over a wide range of patient population. These studies have also provided strong leads for work designed to answer the question of appropriateness of a given drug for a particular type of patient. It is apparent that an understanding of the effects of new drugs on brain and body chemistry is required for a rational approach to the use of such drugs in the treatment and control of mental and emotional disorders. Such studies in animals are needed to pave the road for more sensitive and systematic approaches in humans.

The Institute's research activity is aimed in large measure at a number of special problem areas which demand either new or expanded effort. Toward this end, the recent reorganization of the Institute has resulted in the establishment of a number of Centers designed to integrate and coordinate work in fields of importance—such fields, for example—suicide, to be given comprehensive attention through the Institute's Center for Studies of Suicide Prevention. Other fields include mental health and social problems, and schizophrenias. Similar comprehensive efforts are being directed toward the solutions of problems of alcoholism, narcotic and drug abuse, mental health problems of children and youth, and crime and delinquency. These latter are discussed as part of the Institute's Special Mental Health Programs.

In the prevention of mental illness and the improvement of mental health, it is no longer enough to search for the causes of the mental illnesses after disability has developed. Great emphasis must be placed on prevention—on learning how to intervene at the places of stress and the times of crisis to prevent mental illness. To approach this task, the mental health laboratory has been enlarged. The lab still has its test tubes and pipettes, its rat mazes and its primate centers. But today it also encompasses people crowded into urban slums and isolated in rural cabins. Scientists and clinicians have become increasingly aware of the relevance of social considerations to the study of illness and health. The manifestations of mental disorders overwhelmingly involve disturbances in personality functioning and interpersonal transactions, and these in turn have widespread and significant social repercussions. Clearly, the phenomena of mental illness make themselves known, as do no other pathological states, primarily through behavior, and moreover, through the behavior of the entire human organism, wherever found—at home, at work, at school, at leisure time activities. A growing number of research programs, therefore, focus on emergent social problems—areas such as marriage and divorce, school mental health, cultural deprivation, the behavior of the mentally ill offender, mass violence, and problems of urbanization and metropolitan life. These and other areas are receiving specal and coordinated attention through the Institute Center for Studies of Mental Health and Social Problems, and through the Center for Studies of Metropolitan and Regional Mental Health Problems.

Through its program of applied research, the Institute continues to pursue one of its primary goals: The prompt and effective application of research findings and other new knowledge leading to improved ways of preventing, diagnosing, and treating mental illness and strengthening mental health. An important means for accomplishing this goal is the utilization of available community and institutional resources, through which the Institute sponsors a broad range of applied research activities and pilot activities. As a result of the combination of both fundamental and applied research projects, a number of pioneering innovations are being tested, and new concepts in mental health services are being realized in practice.

The goals of prevention, early diagnosis and early treatment continue to guide the work of the program. Efforts to meet the needs of patients requiring such care are being made by the Institute in orphanages, foster homes, hospitals for the mentally and emotionally disturbed, correctional institutions, and various other agencies. These efforts are crucial in the struggle to overcome the forces that perpetuate mental illness, intellectual retardation, and antisocial behavior, that prevent so many persons from realizing their capacities as human beings. Institutions where we place our mentally ill can compound the problem instead of easing it. Consequently the Institute supports a variety of research projects to learn and show how institutional and community services can be integrated and improved. A number of studies are being directed, too, at improving the welfare of patients outside the hospital.

The Institute's program of applied research also serves to develop fundamental knowledge gained through basic and clinical research or through experience to

the point where it may be used in the delivery of mental health services. Project methods extend from experiments on the relative efficacy of different service techniques to the field testing of new operating service programs. In all projects evaluation of the efficacy of the service or of its process of delivery is stressed.

Investigators have explored new ways of remotivating and rehabilitating chronically and severely ill mental hospital patients, and have developed effective techniques of caring for patients and providing mental health services in the community. Epidemiologic data have been collected on which to base needed services, and to help evaluate the effectiveness of community mental health programs. In the areas of preventive work, the impact of psychiatric services on general medical care has been studied.

Emphasis will now be placed on stimulating the application of a systems approach in the development of models of integrated mental health services. Studies will be instituted to trace the patterns by which services are sought and by which they are provided in order to develop new models of service. Studies of community process will be used to improve communication and cooperation among helping agencies. The ultimate goal of these new studies is to improve the decision-making process in determining treatment of choice, to increase the number of alternatives that are available to the person in need of help, and to develop coordinated programs of community mental health and related services. Such programs should be planned to facilitate their use by appealing to and being based on the needs of those who need help.

Applied research projects continue to provide significant innovations in mental health programs. These projects have demonstrated the practical effectiveness of new methods of treatment and have become models for replication.

Clinical Research Centers

The clinical research centers program provides for a comprehensive, multidisciplinary approach to the enormously complex problems of clinical research. Funds specifically for this program are used to maintain the facility itself; the research which is carried out at the centers may be supported by long-term research grants to individual investigators, working on inter-disciplinary research programs.

Three major centers being supported are devoted to the study of adult psychoses—primarily schizophrenia. One program focuses on longitudinal studies of chronic schizophrenics with the aim of uncovering underlying periodicites in specific physiological systems. Investigators have found thyroid medication beneficial in a number of cases of periodic catatonia, a condition in which the patient shows cyclic variations in activity, from excitement to inactivity or stupor. Another program involves a metabolic ward maintained for biological studies of acute psychotic disorders; the purpose of the research program is to integrate studies of the relationships between metabolic, physiological, and behavioral factors. Investigators have identified an atypical amine in the urine of schizophrenic patients, a finding which suggests a defect in biological transmethylation associated with schizophrenia. A third program entails an intensive study of chronic schizophrenics. Data are being gathered to provide a continuous picture of the patient's functioning on the ward, his mental status and mood, and his response to drug treatment and psychotherapy. Physiological correlates of the patient's behavior are provided by a telemetry system and psychoendocrine studies.

Psychiatric treatment is the emphasis of a number of clinical research centers. One consists of a 20-bed ward in a large psychiatric facility, and research is focused on the therapeutic process. In the present phase of the study, patients who have not responded well to treatment in the past are given intensive, individual, psychoanalytically-oriented psychotherapy. Another center is devoted to the study of childhood schizophrenia. The autistic children live in the wards during the week, with weekend home visits an important part of the regimen. A behavior therapy approach is being used, for it has been found that by intensive operant conditioning, the behavioral repertoire of these children is enlarged. Studies of the biochemical and physiological makeup of these children—studies of cerebral-evoked responses, sleep and dream patterns and dietary intake—as well as studies of social interaction are being carried out. Also investigators have completed gathering data from families with normal children for a comparison with their patients' families.

Effort is being made to initiate more clinical research centers in medical centers with already well-established research programs. Much can be learned about

mental illness from a concerted, systematic approach which describes the natural history of the disorder, investigated its physiological and biochemical correlates, and assesses the effectiveness of various treatment regimens.

An increase of $83,000 will provide for two additional positions and increased other objects support required to strengthen the grants management review activities for these areas of research.

Included in the net increase is $7,000 for mandatory items such as annualization of positions new in 1967, offset by non-recurring items and $6,000 for one less day of pay in 1968.

INTRAMURAL RESEARCH

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	519	$5,256,000	526	$5,278,000	+7	+$22,000
Other expenses		8,369,000		10,836,000		+2,467,000
Total	519	13,625,000	526	16,114,000	+7	+2,489,000

The Intramural Research Program of the Institute is devoted to a broad series of investigations of the fundamental biological, psychological, and social processes which underlie the mental disorders, and to clinical studies of the mental disorders. Included are explorations in depth of a variety of treatment methods—from psychological approaches to the employment of pharmacological agents. The goal of these studies is to define as specifically as possible the circumstances in which the various therapeutic interventions are most effective. At the same time a broad and multidisciplinary program of investigations is being carried out with a view toward defining those aspects of heredity and environment which shape behavior, and toward discovering those body structures and psychological and physiological processes which finally determine the adaptive and maladaptive nature of the individual's response. Knowledge gained from such studies will contribute both to the foundation of a truly preventive psychiatry and to an understanding of the conditions necessary for the most creative development of human resources.

Studies of the role of the catecholamines in normal and abnormal behavior have been pursued more intensively during the past year. It has been found in the clinical laboratories that alterations in the metabolism of these biogenic amines is a sensitive indicator of stress. In biochemical laboratories, the mechanisms of this increased metabolic activity have been determined, and some of the enzymes involved have been identified. It has been found that various psychotropic drugs exert their influence at different points along the metabolic pathway. In the neurophysiology laboratories, using combined electro-physiological and pharmacological techniques, direct evidence was obtained linking norepinephrine to a transmitter funcion in the central nervous system.

In parallel studies, the influence of electrolytes on behavior and on central nervous system activity is under investigation. The dramatic amelioration by lithium of the manic phase of the manic-depressive reaction has been confirmed; it seems also to prevent the development of the depressed phase.

In the psychological and social area, a broad area of research concerns in general, the ways in which individuals develop their perception of the world about them and how values are formed and changed. It is clear that the family in the crucial setting in which he individual learns to perceive and organize his experiences, to construct concepts of reality, and to establish values concerning himself and others. The ground-breaking studies of families with schizophrenic members are being deepened and extended to include other types of mental illness, somatic illness, and behavioral disorder. It seems clear now that therapeutic programs which take some account of family communication patterns show considerable promise.

Studies have revealed the profound influence that parental behavior and values exert on the child's development. The baby's earliest responses, it is now clear, can be significantly altered by changes in the behavior of those who take care of the baby,. Cross cultural and other studies of infants as young as three to four months reveal clear differences that are related to the different patterns of mothering. Longitudinal followup have shown that these learned patterns of

response persist to at least two and a half years; the children will be observed again at age six to see whether their response patterns have become enduring behavioral and psychological traits.

At the NIH Animal Center a habitat has been designed to study the effects of crowding on experimental animals—in this case on populations of wild and tame rats. Attention will be directed to such processes as aggression, social withdrawal, and the origin of altered types through natural selection. In 1968 two small laboratory buildings will be completed to house research on animal learning and on behavior under semi-natural conditions. Here studies of the neurophysiological and endocrinological correlates of such vital forms of behavior as foraging, socializing, mating and rearing young will be carried out. New light on the physiology of mood will also result, a problem important for understanding the psychoses, but one which is difficult to carry out in a controlled laboratory setting.

The problem of combating narcotic addiction would be simplified if a successful narcotic antagonist could be discovered. A promising one now being investigated is naloxone, which in animals has turned out to be a stronger analgesic than morphine and more potent antagonist than nalorphine; furthermore, it produces no subjectives effects, and creates no physical dependence. Its practical utility is being vigorously explored, but its existence does demonstrate that the euphorogenic and physical dependence producing properties of drugs can be dissociated from their analgesic activities. Another narcotic antagonist, cyclazocine, after intensive laboratory study is now undergoing clinical field trials in several treatment programs. It has been shown that this drug can be administered to post addicts in sufficiently large doses to make them immune to the euphoric effects of narcotics and to prevent them from becoming physically dependent. Initial results as a method of treatment are promising.

Other drug studies are concerned with the physiological, biochemical, psychological and social factors involved in addiction. One interesting development is the validation of conclusions drawn from earlier studies that addiction to narcotics may produce long lasting changes in physiological functions and behavior which continue for prolonged periods following termination of drug use. As long as four months after withdrawal there are still abnormalities of respiration, temperature and circulation. Such physiological abnormalities also characterize the addict who has developed tolerance to a narcotic. In another part of the addiction research program plans are being developed for followup studies of the social and cultural factors associated with addiction in the communities where the addicts live. It is hoped that information obtained from these community studies, coupled with what has already been learned from hospitalized addicts, will produce important data concerning the factors associated with relapse and with continued abstinence. Information of this type is essential to the development of methods for increasing the number of former addicts who remain abstinent.

Alcoholism as a form of addiction will be investigated both clinically and experimentally in a series of studies on the biological, biochemical and behavioral factors which are responsible for it. Metabolic and endocrine processes related to both intoxication and withdrawal will be studied in alcoholic patients along with analysis of the patients' behavior. Drinking patterns of alcoholics will be investigated. Finally, in order to get at some of the biological aspects of alcoholism that cannot be studied in human subjects, an animal preparation which meets the pharmacological criteria of addiction to alcohol will be developed.

Research on depression and suicide includes a number of behavioral, biochemical, and biophysical studies related to the causes of depression, the mechanisms by which present treatments work, the discovery of more effective forms of treatment, and the search for more reliable ways of predicting suicidal intent. An examination of sleep patterns in depressed patients has shown that the extent of sleep disturbance is highly related to clinical estimates of depression. There have been further indications that marked disturbances of the "dreaming sleep" function at certain stages of depression may be implicated in the development of psychotic symptoms.

In the late 1950's Institute scientists were successful in being able to separate into two componets the enzymes which convert phenylalamine, a constituent of our food, to tyrosine. This discovery was of unique interest because it was imperfections in this conversion, resulting in the development of phenylpyruric acid which caused phenylketonuria (PKU), a disease which causes severe mental retardation. Following upon this important finding was the development of tests

which permit early detection of this disorder in the newborn child. When detected it is possible to prescribe a phenylalamine-free diet for the first years of the baby's life, resulting in the prevention of this disorder.

None of these inborn metabolic errors is common; individually most of them are even quite rare. On an aggregate basis, however, the inborn errors assume significance as a cause of mental retardation. No price tag can be put on the salvaging of a child's brain, and on enabling him to live a normal productive life. It is possible, however, to estimate savings to the taxpayer resulting from some of the research on the inborn errors problem. The cost of lifelong institutional care and treatment of a phenylketonuric retardate—generally at community expense—would probably run at least $100,000. Detecting and treating just one or two children with PKU, for a lifetime, would pay for an entire year's early screening of all newborns in one of the states.

Study is continuing of the disease homocystinuria, another disorder resulting in mental deficiency. This is one of several diseases which are due to defects in the metabolism of sulfur-containing compounds. A related disease called cystathioninuria has now been studied and has been shown to be characterized by the lack of two enzymes—cystathionase and homoserine dehydratase. Future work will concentrate on discovering the factors which regulate the levels of these enzymes in the cell, and which must be known before the diseases can be effectively treated or prevented.

A program increase of 7 positions and $1,860,000 includes $500,000 for renovation of clinical center space for psychiatric research; $450,000 for additional data processing and computer facilities; $210,000 for equipment for the expansion of the neurochemistry laboratory; and $700,000 for expansion in the intramural research programs including animal behavior studies related to learning, problem, solving, environmental factors, etc., as well as longitudinal population studies of the Norway rats; studies of the metabolism of addicting drugs in man, field follow-up studies of former drug addict patients; and normal increases in costs of on-going research programs.

Included in the net increase is $37,000 for annualization of positions new in 1967, offset by non-recurring items and $13,000 for one less day of pay in 1968. Also included is an increase of $642,000 for centrally furnished services from the "National Institutes of Health Management Fund."

MANPOWER AND TRAINING

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	87	$945,000	87	$945,000		
Other expenses		708,000		758,000		+$50,000
Total	87	1,653,000	87	1,703,000		+50,000

The training program has as its primary objective the increase in the numbers of mental health specialists and the improvement of the quality of their training. The scope of the program extends from those disciplines traditionally recognized as constituting the "core" of mental health manpower, to subprofessions, technicians, and a wide variety of ancillary personnel who are significantly involved in activities relevant to mental health and mental illness. Training support is available at the graduate, undergraduate, and postgraduate levels both for generic training and in special areas such as alcoholism, aging, juvenile delinquency, corrections, etc. An orientation to the community mental health approach is encouraged throughout. Experimental and special projects are supported in all fields to develop new and innovative programs of training in mental health skills. Training opportunities are provided for development of skills in research, clinical services, training, administration, and consultation in mental health. Recently, concentrated effort has been directed to development of a program of continuing education intended to upgrade and update the skills and knowledge of professionals already in the manpower pool.

Since its inception the Institute's training program has played a major role in the development of the national mental health manpower pool. The expansion

which has occurred in the manpower pool makes feasible many of the newer programs developed. In addition it is this expansion which makes possible the attainment of the major goals of the training program. The table which follows gives an indication of the growth of the mental health manpower pool.

Mental health manpower pool

	1950	1960	1965
Psychiatrists	5,500	13,000	18,593
Psychologists	3,500	9,000	13,265
Psychiatric social workers	3,000	7,200	11,378
Psychiatric nurses	10,000	15,000	20,554
Total	22,000	44,200	63,790

Since a major goal of the program is to produce over 87,000 trained "core" professionals (psychiatrists, psychologists, social workers, and psychiatric nurses) by 1970 it is apparent that there is still much to be accomplished. From this pool will come the personnel to staff the comprehensive community mental health centers research, laboratories, universities, and to meet the needs of other institutions and activities for mental health personnel.

In 1967 increased attention was given to training programs which could best serve the development of a national community mental health effort. Encouragement has been given to training modifications and innovations incorporating new knowledge and techniques through the medium of experimental and special projects. Ground work has been laid for expansion of the continuing education aspects of the program, formerly limited to improving the psychiatric skills of non-psychiatric physicians. In general, mental health training centers have demonstrated their capacity and interest for increasing their training productivity and a budget increase of $8,367,000 over the 1966 level has provided the means for growth.

The graduate training program of the Institute will continue to be a major resource in the development and improvement of centers for the training of mental health professionals. The program has been the catalyst which has accelerated the production of professional mental health manpower, by enabling larger numbers of trainees to pursue graduate training and by enabling training facilities to expand their capacity, and it has benefitted each of the professions involved further because of the assistance in improving general quality of teaching programs.

In 1967 a significant proportion of the increase in funds is being used to provide for program expansion and increased numbers of trainee stipends in the mental health disciplines. In addition to the continued expansion of established programs, the funds have also been utilized to incorporate into training the elements of community mental health, for psychiatrists, psychologists, nurses, and social workers. The support of experimental and special projects has also been increased in order to continue the emphasis of initiating new departures in training and the dissemination of innovative procedures. These projects have provided the means for developing new kinds of mental health workers and training for persons from allied disciplines.

Research training continues to receive expanded emphasis because of the need for personnel trained to investigate problems of human behavior and its disorders. The information generated by research supports clinical service in all fields. Research training programs are included not only within the four major disciplines, but in the biological and social sciences as they relate to mental health.

The general practitioner training program continues to provide support for stipends to "general practitioners" who wish to become psychiatrists, and to non-psychiatrist physicians who wish intensive short-term training in psychiatric principles. The third element of the "GP" program, which provides continuing education courses for non-psychiatrists, has been incorporated into a new and more comprehensive effort, the Continuing Education Program, which will develop a national program to provide continuing training for all levels of mental health personnel and to increase the mental health training of personnel in allied fields.

It is proposed that in 1968 the total graduate program, including clinical training in the regular program, research training, the general practitioner program, and the experimental and special training grants in all areas, increase from $70,348,000 to $75,600,000, an increase of $5,252,000.

In undergraduate training, efforts in psychiatry serve to supplement the general preparation of all physicians, and have already influenced increased numbers of medical school graduates to enter psychiatry as a specialty. The program, by 1965 had reached all schools of medicine and osteopathy in the United States, and had made possible full-time faculties in numerous departments of psychiatry, making possible great improvements in the quality of teaching. When grants are made to medical schools in their developmental stages, the result has been to place psychiatric faculty at the core of the planning operation enabling them to participate in establishing the philosophy of entire schools in addition to the psychiatric training program. Support of the teaching of the behavioral sciences has made possible the integration of behavioral sciences into preclinical and clinical training of the modern physician.

Increases in undergraduate support in nursing will continue the effort begun in 1965 to provide trainee stipends for the final two years of prebaccalaureate training in preparation for graduate study in psychiatric nursing. This program is intended to increase the pool of candidates prepared for graduate education in mental health nursing or other graduate education in mental health.

Undergraduate research training in psychology represents an experimental effort to explore training for academic-professional integration prior to graduate school. Varied programs have been initiated in a variety of settings as a basis for exploring the value of this type of training.

The undergraduate program would increase from $8,500,000 to $9,000,000 in 1968. The increase will be used primarily to further the development of the undergraduate psychiatric nursing program, to raise the size of awards for teaching costs in the undergraduate psychiatric program, to increase the numbers of medical student research stipends, and to meet the needs for further support of the undergraduate human behavior program.

It is anticipated that there will be an early demand for continuing education support for the general purpose of counter-acting obsolescence of skills, and additionally to prepare personnel to participate in areas of current emphasis, e.g., community mental health, delinquency, alcoholism and drug abuse. Priority will be given to projects with one or more of the following emphases:

(1) development of strong continuing education divisions within training centers for the mental health professions, increasing the amount and quality of continuing education resources available in the vicinity; (2) continuing education which is an integral component in the implementation of community and State mental health planning efforts; (3) projects with a program development emphasis, targeted to the needs of a specific group of potential trainees, as compared to offering isolated courses to whomever may be recruited; and (4) evaluation projects, preferably built into active continuing education and staff development programs.

Research fellowships: Research fellowships provide support for the training of behavioral and biomedical scientists to investigate the problems of mental illness and of mental health. Research career development awards recruit promising young scientists to research on mental health problems, support them in full-time research, and research career awards enable experienced investigators to pursue research careers in stable positions.

Fellowships are awarded to graduate students preparing for research careers, to recent Ph. D.'s and graduates at an equivalent level who wish to acquire additional knowledge and skills, and to experienced scientists who require additional study or preparation for a specific development in experimental work. Basic scientific training, training for specific projects, and advanced training for deepening mental health research by biomedical and behavioral scientists are all effective functions of the Institute fellowships program. The research fellowships program has developed outstanding research talent in a variety of areas essential to the understanding of factors contributing to the incidence of mental disturbance or illness. Continuing and expanding this program is the plan for 1968. The requested increase in funds of $672,000 would provide for 116 additional awards, mainly at the predoctoral level, representing, currently, the greatest demand and opportunity for financial support.

Analysis of research being conducted by investigators with research career program awards demonstrates a broad scope of interests and a considerable variety of approaches to mental health problems. Studies are being made of such

factors as the role of life history factors on the development of schizophrenia, mechanisms underlying the psychosomatic illnesses, brain chemistry and chemical alterations resulting from the administration of drugs, patterns of emotional development, the psychology and psychophysiology of sleep and dreaming, relations between endocrine and behavioral processes, and behavioral processes from sociological and anthropological points of view.

In 1968, this Institute will continue the support of mental health career investigators and expand the program by new awards. With additional funds in the amount of $54,000 the requested appropriation would provide for 116 continuations, and for 5 new research career development awards.

An increase of $50,000 will provide for contracts for studies of mental health manpower needs.

MENTAL HEALTH SERVICES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	81	$887,000	81	$883,000		−$4,000
Other expenses		667,000		667,000		
Total	81	1,554,000	81	1,550,000		−4,000

The mental health services programs support a broad array of programs aimed at the improvement of the delivery of services to the mentally ill. These programs include:

1. The support of construction and staffing of comprehensive community mental health centers.
2. The improvement of the quality of care and competence of staff in state mental hospitals and institutions.
3. The administration of the mental health care administration aspects of the Social Security legislation.
4. The improvement of planning for comprehensive mental health services, and integration of mental health planning in the comprehensive health planning.
5. The coordination of Institute programs of regional, metropolitan and rural mental health.

Mental Health Care Administration: Created, in response to a long-felt need, the Mental Care Administration Branch will concentrate its activities on three major areas to promote the mental health aspects of the Social Security Amendments of 1965: Program Development, Certification and Consultation and Standards Development.

Studies have reported that over 25 percent of the 65 year old and older population (19 million people) have a psychiatric disorder which warrants intervention and that about 15 percent of persons in this age group have severe mental disorders. Approximately 55,000 aged persons are admitted to State hospitals alone each year and public and private psychiatric hospitals have a resident population over 65 years of age of over 150,000 people.

One of the major responsibilities of the Branch will be to take a leadership role in activities designed to insure that appropriate psychiatric services are available for persons requiring geriatric psychiatric care and treatment.

A recent survey of all general hospitals in the country revealed that only 17.3% routinely admitted psychiatric patients for treatment. An even smaller percentage provided an intensive and comprehensive treatment program for the aged mentally ill.

Active collaborative endeavors with the Social Security Administration and with national standard-setting professional organizations will have two main objectives; to increase the number of qualified providers of psychiatric services and to maintain quality control.

At the same time an intensified consultation and education program is required at the regional, state and local level to upgrade the scope and quality of treatment programs and to incorporate public and private hospitals, extended care facilities, community mental health centers and home health agencies into an effective mental health service program.

Studies of Metropolitan and Regional Mental Health Programs: Established in July 1966, the new Center for Studies of Metropolitan and Regional Mental Health Problems has as its mission the exploration of the interrelationships between the Nation's metropolitan areas and the mental health of the more than 60% of American people living within those areas.

The first six months of the Center's operation have been devoted to surveying the field, opening channels of communication with other Federal agencies, and developing its program. A few Institute-supported projects which were already underway and are directly related to this subject area were transferred to the Center. They involve investigations of the dimensions of some characteristically urban problems—neighborhood blight, urbanization of migrants, and homelessness.

The developing program of the Center is based on the overriding importance of fostering at the metropolitan area and regional levels the primary prevention of mental illnesses. The need is to introduce mental health considerations into every area of urban development, both physical and social. Toward that end the Center's training and research programs are being designed to produce better understanding of the phenomonology of urban life and the points of intervention through which mental health can be fostered.

Examples of the investigations the Center will seek to support in the coming year are: psycho-social reactions to physical and social density, an evaluation of community organization techniques in core central cities, modes of integration of mental health planning and urban development planning, and the dimensions of "community" as a viable concept of social organization in the urban setting.

Hospital Improvement Projects: The purpose of the Hospital Improvement Project program is to provide support for demonstrations of improved methods of care, treatment, and rehabilitation of the mentally ill and mentally retarded in State mental hospitals. Its objectives are to improve therapeutic services and the quality of patient care, and to strengthen the role that State institutions can play as the comprehensive community mental health and mental reardation programs unfold.

The program was initiated in 1964. At the end of last year, 145 of our 302 State hospitals received awards through the program; among the 138 State institutions for the mentally retarded, 89 were the recipients of grants.

Eighteen States have grants for all of their eligible institutions in both categories. Every State has at least one hospital improvement grant. Only three States have no grants for any of their mental hospitals, and three other States have no grants for their institutions for the mentally retarded. Fifty-three percent of the institutions eligible to apply for hospital improvement grants have received them in the three years since the program was initiated. Two-hundred and twelve institutions have received both Hospital Improvement and Inservice Training Grants. There are now over 50,000 patients involved in current hospital improvement projects. New program development is only one aspect of the potential of this grant program. There are many indications that when an institution has been able to achieve a better therapeutic program and to stimulate staff into new ways of doing things, the gains made spread to other aspects of the Institutions' program and are likely to be irreversible.

During 1967, the Hospital Improvement Project program for institutions for the mentally retarded is being transferred to the Division of Mental Retardation, Bureau of Health Services, Public Health Service.

Over 80 percent of the funds in hospital improvement projects are spent for personnel to provide new therapeutic services. A major emphasis in mental hospitals has been placed upon programs that would improve treatment, training, and rehabilitation of the long-stay more severely ill.

A number of hospitals are developing treatment services for special groups, such as the aged, emotionally disturbed children, adolescents, or mentally ill prisoners. For example, in 22 States, hospital improvement grants have been used to support treatment services for emotionally disturbed children and adolescents in mental hospitals. In several States the grant has allowed the State to establish for the first time specialized services for children.

Some hospitals are using projects as one step in the reorganization of hospital service and the development of geographical based units. These units provide intensive care as well as longer term treatment for patients coming from a specified geographical area. They assist the hospital to become involved with community facilities in the area to achieve initial steps in the development of comprehensive mental health services.

While the progam is still too new for a formal assessment of its impact on patients, it is already clear that many of the severely disturbed "back ward" custodial patients are responding positively to the new treatment programs. This response is raising expectancies of what can be accomplished with "chronic" patients. For many of the institutions, projects are stimulating and assisting in the development of improved hospital-community coordination and the more effective use of available resources.

Over the past ten years, there has been a revolution in the human climate in many State hospitals. There have been changes in the role of the patient, changes in expectation as to patient behavior and changes in relationships between staff and patients and amongst staff. Not all hospitals have participated equally in this humanizing atmosphere. It is these hospitals that the hospital improvement program is designed especially to reach.

Inservice Training Program: The long range objectives of the Inservice Training Grant Program are to increase the effectiveness of staff in mental hospitals and institutions for the mentally retarded and to translate increasing knowledge into more effective services to the residents of these institutions. Major emphasis in this program has been placed upon training psychiatric aides, attendants, house parents and others similarly involved in direct patient care, since they constitute such a large and important treatment resource in mental hospitals and institutions for the mentally retarded.

During the first three years of operation of this program, inservice training grants were awarded in 181 State mental hospitals and 99 institutions for the retarded. This is 64 percent of all institutions eligible to apply. At least one inservice training grant has been made to a facility in every State. Twenty-one States have received grants for all of their eligible institutions. Forty-nine States have inservice training grants in at least one mental hospital; and institutions for the retarded in 45 States have been awarded inserive training grants.

Funds for 1966 were distributed as follows: 181 inservice training grants to mental hospitals totaling $4,171,028 and 99 inservice training grants to institutions for the mentally retarded totaling $2,182,000. During 1967, the Inservice Training program for institutions for the mentally retarded is being transferred to the Division of Mental Retardation, Bureau of Health Services, Public Health Service.

Primarily, four types of training are being provided under inservice training grant support. These are refresher training, continuation training, supervisory training, and instructor training. There are over 10,000 trainees directly involved in current projects.

A primary goal in the use of inservice training funds has been to prepare employees to work in new treatment programs and to achieve more positive attitudes and better understandings of the patient and his potential for recovery. Several mental hospitals have initiated training programs for employees recruited from new sources, such as high school students in vocational education programs or students from a nearby college, or they have provided training for community personnel working closely with the hospital.

Special attention has been given by the Institute's staff to planning and conducting regional conferences on inservice training collaboration with state and local inservice training personnel. In general, these conferences have been focused on assisting state and local inservice training personnel to develop their programs and in providing information on teaching method, curriculum development, administration, and evaluation. Conferences of this nature were held in seven of the nine DHEW Regions during 1966.

Mental Health Facilities: The staff of this branch is responsible for the Institute's program of assistance in the construction of community mental health centers. This program is discussed in the "Community Mental Health Resource Support" appropriation which follows.

Community Mental Health Centers Staffing: The staff of this branch is responsible for the Institute's program of assistance in the staffing of community mental health centers. This program is discussed under the "Community Mental Health Resource Support" appropriation which follows.

Included in this activity is a decrease of $4,000. An increase of $11,000 for annualization of positions new in 1967 is offset by nonrecurring items such as one less day of pay.

SPECIAL MENTAL HEALTH PROGRAMS

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	147	$1,676,000	159	$1,768,000	+12	+$92,000
Other expenses		611,000		1,472,000		+861,000
Total	147	2,287,000	159	3,240,000	+12	+953,000

The objective of the Institute's Special Mental Health effort is to plan and administer programs directed toward specifically identified problem areas of special significance such as alcoholism, narcotic and other drug abuse, mental health of children and youth, crime and delinquency, and suicide prevention.

Each of these areas possesses certin common characteristics. They each are areas of critical public importance; they each require a multidisciplinary approach both in the conduct of research and delivery of services; in most areas, relatively little is known about underlying causation, and they all have requirements for additional specialized manpower in order to adequately respond to the requirements for new knowledge and improved patterns for the delivery of services.

In order to respond to the requirements of these special areas, and to better utilize the resources available to it, the Institute has developed a group of specialized centers to be charged with responsibility for the total Institute program activity in each of these key fields. Accordingly, these centers, now in the early stage of implementation, will serve as the national focus for research, manpower development, and services delivery in their fields.

NATIONAL CENTER FOR PREVENTION AND CONTROL OF ALCOHOLISM

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$4,288,000	$4,500,000	+$212,000
Training grants	256,000	430,000	+174,000
Fellowships	31,000	35,000	+4,000
Direct operations	477,000	698,000	+221,000
Total	5,052,000	5,663,000	+611,000

The conception of alcoholism as a disease entity has gained public and professional acceptance during the last two decades. Health professionals have led the way, incorporating scientific and humanistic principles into their approach to alcoholism. More recently, our judiciary has taken cognizance of this contemporary approach, and courts are beginning to regard the alcoholic as a sick person in need of medical attention. In addition, our ultimate understanding of alcohol addiction will require the contributions of the social and behavioral sciences as well as those of biological disciplines.

Alcoholism is not an all-or-none disease but one composed of many subspecies. No formal definition of alcoholism is universally applicable because the disease is defined in part by the socioeconomic context in which it occurs. Thus, the person regarded as an alcoholic in a northern industrial city may not be seen as such in an isolated rural area. With certainty, however, alcoholism in all its subspecies is conspicuously present in virtually all socioeconomic groups in all contemporary cultures. While the reliability of our current data on alcohol-related problems is limited, certain findings suggest the extent of the overall problem.

It is estimated that there are between four and five million alcoholics in the United States. If one includes their families, perhaps 20 million people are directly affected by alcoholism. According to the World Health Organization, the United States has replaced France as the nation with the world's highest incidence of alcoholism.

Only a small proportion of all alcoholics—perhaps as few as 8%—are of the so-called "Skid Row" type. The vast majority in the United States are living

with their families, holding some kind of job, trying to keep a place in their communities. In 1964, some 11,000 deaths were attributed officially to alcoholism, but the actual number is believed to be far larger. Insurance companies calculate that the alcoholic's life expectancy is ten to twelve years less than that of the average person.

In some states, it is claimed that communities spend $50,000 to $100,000 in support of an alcoholic and his family during his lifetime. Costs to industry have been estimated at a minimum of $2 billion a year.

Alcoholism is the number one mental health problem in nine states, according to hospital diagnoses. Of the first admissions to state and county mental hospitals in 1963, one in seven was diagnosed as alcoholic. One out of every eight male patients seen in outpatient psychiatric clinics had an alcohol-related diagnosis.

In recognition of the magnitude and social impact of this problem, the National Center for Prevention and Control of Alcoholism has been established by the Institute to coordinate the Public Health Service activities in alcoholism, to formulate new programs, and conduct research studies in its own laboratories. Its general functions are:

(1) To provide leadership in planning and developing national programs concerned with alcoholism, in collaboration with other Federal agencies, national organizations, state and local governments and voluntary citizens' groups;

(2) To coordinate Institute research, training and service activities in the field of alcoholism;

(3) To foster the development of a wide range of basic and applied research studies of the interrelated biochemical, psychological, behavioral, clinical, pharmacological aspects of alcohol use;

(4) To coordinate and stimulate statistical and biometric programs for epidemiological and longitudinal studies of alcoholism and alcohol use;

(5) To accelerate the application and research findings through consultation, demonstrations, field trials, and other mechanisms;

(6) To assist national, state and local organizations in improving and extending programs for the prevention of alcoholism and for the care, treatment, and rehabilitation of alcoholics;

(7) To give leadership in the development of inservice training and the continuation of post-graduate training to accelerate the use of current and new knowledge;

(8) To promote health education programs about alcohol for the general public by stimulating the development of educational materials and including pamphlets, books, and audio-visual methods.

The stimulation of new comprehensive training programs will receive high priority from the new Center. A major deficit in all alcoholism programs—research, training, and service—has been the lack of trained people to carry out the many tasks. Professional training has been sadly neglected. Physicians are usually poorly prepared to handle alcohol-related problems when they meet them in their internships and residencies, and few investigators in basic science disciplines seem to appreciate the possibilities for research in alcoholism. It is reasonable to predict the future advances in our understanding and treatment of alcoholism will depend critically on supplementing and expanding current training programs for professionals. The Center will now initiate support of fellowships to provide stimulation for training personnel to engage in research and other activities in the field of alcoholism. Similarly, expansion and improvement of treatment services depend on the creation of adequate training programs for non-professionals.

Alcoholism is caused by a complex interaction of biological, psychological, and sociological factors. Because of this, the hope for developing a better understanding of the cause, natural history, and eventual cure of alcoholism lies in investigators from a number of disciplines working together as a team and directed toward a common goal.

A matter of high priority for the National Center for Prevention and Control of Alcoholism will be the development of university-based multidisciplinary research centers for the study of alcoholism and alcohol-related problems. At the present time only one such center exists in the United States (Rutgers University).

During the current year, staff of the Center will consult with a number of medical schools and universities to aid in preparation of program project grant

applications for establishment of multidisciplinary alcohol research centers. To date one such application has been received, and three additional applications are expected by March 1, 1967. These four new applications combined with a renewal application are a promise of the development of five university-based alcohol research centers.

Although the focus of research proposed will differ between the five research centers, all will have the following common general features:

1. Research will be multidisciplinary in character with integration of basic science and clinical science disciplines. Participating disciplines will include psychiatry, social psychology, experimental psychology, biochemistry, neurophysiology, and a variety of medical sub-specialties such as cardiology and gastroenterology.
2. All of the centers will conduct an active program of research training at the post-doctoral level in medicine and the various basic science disciplines.
3. The research centers will be located in geographical areas which have a high endemic incidence of alcoholism. The establishment of centers in these areas should provide more incentive for training, research, and service by virtue of the stimulus they will offer to the university and the community at large.
4. All of the research centers will be associated with universities and medical schools which have demonstrated excellence in carrying out research and treatment for many disease entities.
5. The centers will have wide geographical distribution within the United States.
6. The principal investigators and project directors at the centers will be distinguished scientists who have carried out research of high quality in the field of alcoholism.

During fiscal year 1968, it is anticipated that at least four more requests for establishment of alcohol research centers will be submitted by universities and medical schools in New York City, Chicago, New Orleans, and Dallas. It is likely that additional requests for establishment of university-based multidisciplinary alcohol research centers will be submitted from Los Angeles, and Oklahoma City, during 1968.

The establishment of multidisciplinary research centers is both necessary and appropriate among the disease entities which can be investigated through cooperative and combined efforts of behavioral and biological scientists. Perhaps none has offered so unique a challenge as alcohol addiction. At the experimental research level a variety of new behavioral and biological techniques are available which can be imaginatively applied to alcohol research. Studies which will be carried out at the multidisciplinary alcohol research centers should greatly enhance our fund of information in the field of alcoholism and speed progress toward its prevention and control.

In the Centers' intramural laboratories to be developed in the coming year, alcoholism as a form of addiction will be investigated both clinically an experimentally in a series of studies on the biological, biochemical and behavioral factors which are responsible for it. Metabolic and endocrine processes related to both intoxication and withdrawal will be studied in alcoholic processes along with analysis of the patients' behavior. Drinking patterns of alcoholics will be investigated. Finally, in order to get at some of the biological aspects of alcoholism that cannot be studied in human subjects, an animal preparation which meets the pharmacological criteria of addiction to alcohol will be developed.

Enactment of new health-care legislation doubtless will result in an increased demand for alcoholism related activities. The staff of the Center is prepared to consult and work with state officials to develop such programs. Discussions have already begun with the Department of Justice, the offices of Welfare Administration, the Office of Education, and the Vocational Rehabilitation Administration.

Finally, much remains to be done to improve attitudes toward alcoholism. The disease concept of alcoholism has only recently begun to overcome the social stigmatization usually associated with this illness. Attitudes held by both professionals and the general public must be modified further before significant progress can be made in our ability to cope with the national problem of alcoholism.

CENTER FOR STUDIES OF NARCOTIC AND DRUG ABUSE

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$3,236,000	$4,404,000	+$1,168,000
Training grants	137,000	231,000	+94,000
Fellowships	34,000	37,000	+3,000
Direct operations	229,000	344,000	+115,000
Scientific communication and public education		1,000,000	+1,000,000
Total	3,636,000	6,016,000	+2,380,000

There are no reliable data on the extent of drug abuse. In 1965, the Federal Bureau of Narcotics knew of approximately 60,000 individuals actively addicted to narcotics. This is believed to be a minimal number however, because it is drawn almost exclusively from reports by law enforcement agencies. Far less is known about the prevalance of non-narcotic drug abuse. One estimate is that between 200,000 and 400,000 people may be physically dependent on or habituated to non-narcotic compounds. Tranquilizers, including several with proven addiction potential, are the largest single category of drugs prescribed today. Because these compounds are readily obtainable through legitimate channels, it is especially difficult to cope with their abuse.

Because of the growth of this problem in recent years, particularly among the young, the Institute programs have reflected the increased need for basic and practical knowledge of the biological, psychological and social factors in addiction. The newly created Center for the Studies of Narcotic and Drug Abuse can be expected to enhance the coordination and programming of needed research in this cruical area. A substantial number of laboratory studies, social surveys, and clinical work on addiction are presently supported, with new efforts to be added in these directions.

In the important area of treatment, considerable effort has been expended in the development of controlled clinical evaluations of methods such as maintenance methadone and cyclazocine, and of urinary monitoring of addicts under treatment. In another area, in a study of factors which lead to psychological dependence on narcotics and other drugs in the monkey, it has been found that monkeys will voluntarily inject the same drug which man is known to abuse and to which man becomes addicted. Thus, investigators have developed an animal model in which problems of addiction and the role of environmental factors in abuse can be studied. Another project is currently directed at determining incidence of use of "mindaltering" drugs among college students, the characteristics of frequent users of these drugs, and the consequences of extensive use of the drugs on the social, mental, and physical functioning of these students. Among the Institute's applied research programs, one is now undergoing field testing—a halfway house providing specialized services to addicts, including group therapy sessions, role-training process, and job assignments. A variation of this approach is under study in the form of a neighborhood center which provides counseling, special education, and supervised and unsupervised recreation facilities.

In addition the amounts provided under research grants for implementation of the Narcotic Addict Rehabilitation Act include $504,000 for the development of field testing programs for the treatment of narcotic addiction.

CENTER FOR STUDIES OF SUICIDE PREVENTION

	1967 estimate	1968 estimate	Increase or decrease
Research projects	$2,335,000	$2,600,000	+$265,000
Training grants	250,000	422,000	+172,000
Fellowships	25,000	27,000	+2,000
Direct operations	116,000	186,000	+70,000
Total	2,726,000	3,235,000	+509,000

Suicide, with 20,000 victims each year, represents the tenth leading cause of death in our country. In the 15–19 age group it ranks third as a cause of death, exceeded only by deaths from accidents and cancer; among college students it ranks second. The problem of suicide, however, cannot be measured by statistics alone, for its psychological costs are high to both family and community. In addition to the trauma of death itself, each survivor of a suicide must handle feelings of shame or guilt. No other kind of death in our society carries such stigma, or creates such lasting emotional scars.

The Institute's Center for Studies of Suicide Prevention—now under the direction of the Nation's leading authority in the field—will coordinate an attack on the problem, encompassing support throughout the country of research, training, service, and demonstration activities, as well as direct research programs within the Institute itself. In the interests of a nationwide prevention program, investigators are developing diagnostic and predictive tests to identify those who are high suicide risks—for example, through measurable changes in certain adrenal hormone levels which may serve as a biochemical indicator of suicidal intent in depressed persons. Of special importance is the need to recognize the ways in which potential suicides signal their distress, the warnings they inevitably communicate as they desperately seek support. Two-thirds of those who attempt suicide have recently visited a physician—putting physicians, among others, in a strategic position to identify the suicide's "cry for help" and to respond adequately. Our aim must be not only to improve therapeutic techniques in dealing with the depressed and suicidal patient, but also to develop a large cadre of professionals in the field—physicians, teachers, lawyers, clergymen, nurses, who can respond to the "cry for help."

Work is proceeding on several fronts. The Los Angeles Suicide Prevention Center, in addition to testing methods of providing emergency service, continues to investigate predictors of suicide behavior; one such warning being studied is disturbance of patterns of sleep. In another project, a procedure for providing follow-up care to those who have attempted suicide is being developed and tested at a large hospital. Studies are also designed to obtain patterns of descriptive information regarding experimental factors and interpersonal dynamics which may distinguish the adolescent intent on suicide. In addition, the Institute's work continues to identify possible biochemical indicators of suicidal intent in depressed persons. Increasing research will be stimulated to study the problems of suicidal "equivalents"—that is, social behavior so destructive that it disastrously undermines well-being.

CENTER FOR STUDIES OF CRIME AND DELINQUENCY

Antisocial behavior—ranging from truancy, window-breaking, and petty thievery at one end of the scale to mass murder at the other—is a major problem in our society. Its monetary cost to the Nation has been estimated at more than $20 billion a year. The number of offenders under correctional supervision at any given time is more than one million, close to 30 percent of them in jails, prisons, and reformatories. The number of delinquency cases among youngsters between the ages of 10 and 17 has been increasing considerably faster than the number of youngsters in the group. Recent studies indicate that one out of five boys growing through the age range of 10–17 will appear in juvenile court. This is a nationwide average; in some deteriorated urban areas as many as 9 out of 10 of the juveniles have juvenile court contact.

Criminal and delinquent behavior is symptomatic of troubled individuals and a troubled society. In recognition of the magnitude of the problem, the President has appointed a Commission on Law Enforcement and the Administration of Justice, with which the Institute is working to develop a national program of prevention and control.

Serving as the focal point for the Institute's activities in this field is the Center for Studies of Crime and Delinquency. The Center's efforts to help the Nation control and prevent crime and delinquency include research on the causes of antisocial behavior, the training of professional and non-professional personnel to work with the socially deviant, direct intervention with street-corner gangs and other delinquents, work with offenders in institutions, studies to determine the most effective means of rehabilitation, investigations of the circumstances leading to mass violence, and studies of the factors that combine to produce violence-prone and homicidal individuals.

Current projects include such studies as the examination of distinctive characteristics of delinquent personality types in an effort to define more explicit

treatment and intervention methods; the effect of socially labeling a child as delinquent; factors affecting the capacity to delay gratification and self-control; and the prevention of delinquency by developing predictive measures to identify the pre-delinquent. Community studies are oriented toward the phenomenon of street-corner gangs; direct intervention with delinquent gangs in the community; and adjustment during the post-parole period—a time of crucial importance for recidivism and rehabilitation. One innovative project provides for the development of work opportunities for ex-offenders in programs for crime and delinquency prevention. Studies of the correctional institution deal with its efforts to provide psychotherapeutic intervention—especially through group counseling and mileau therapy. Focus is also placed on the difficulties in changing originally custodial facilities to institutions which are basically treatment oriented. One major function of the Center is to stimulate the communication of information about crime and delinquency.

An important effort in this area is the *International Bibliography on Crime and Delinquency*, a service of the National Clearinghouse for Mental Health Information. This publication for scientific community provides abstracts of the current professional literature and reports of research, demonstrations, and action programs. Future efforts of the Crime and Delinquency Center will focus on the many unsolved problems in this area—for example, on the need for more accurate information on the extent of crime and delinquency; on the development of theories of socially deviant behavior that account for both psychological and social factors; and on the development of more effective and efficient social action programs.

CENTER FOR STUDIES OF MENTAL HEALTH OF CHILDREN AND YOUTH

Recent surveys reveal that during 1963, about 4,000 Americans under 15 years of age and 27,000 between 15 and 24 years were admitted to mental hospitals, both public and private. At the end of the year, 5,000 children under 15 and 25,000 children between 15 and 24 were living their broken lives in these hospitals. Both the first admission rates and the resident population rates for children have increased at an accelerated pace during the last decade—and the rise cannot be explained altogether by pointing to the relative increase in the number of children in the general population. Take, for example, boys between the ages of 10 and 14: In the general population, this group has increased almost twofold since 1950, but it has increased almost sixfold in the mental hospital. No such contrast exists with regard to the American mental hospital population as a whole; here the resident patient rates have declined.

Projections for the decade 1963–73 show that in the age group 10–14, we can expect an increase of 15 percent in the proportion of 10–14 year olds in the country's population; in the mental hospital, however, these children will increase by 116 percent. For older children between the ages of 15 and 24 we can expect a 36 percent increase in the population as a whole, but a 70 percent increase in the wards of mental hospitals.

In public and private institutions for the mentally retarded, 13,000 children under 20 years were admitted for the first time in 1963, while 78,000 such children were residents at the end of the year. Rates for this age group—for both first admission and resident patients—have shown a gradual increase during the last decade.

Data, again from the Institute's Office of Biometry, show that the toll taken by the major mental and emotional disorders is hardly restricted to the adult years. Among public mental hospital resident patients under eighteen, 43 percent were diagnosed as psychotic, 27 percent as retarded or suffering acute and chronic brain syndromes, and the remainder as victims of a variety of personality disorders reflecting both constitutional deficiencies and environmental trauma.

Among children outside the hospital, too, disorders may take forms generally associated with the adult, such as psychoses, neuroses, psychosomatic problems. An estimated 10 percent of public school children in the United States are emotionally disturbed and in need of psychiatric guidance, and at least 250,000 with less serious psychiatric disorders receive services each year at mental health clinics.

Despite the needs reflected in these figures, out-patients clinic data point up the paucity of services available to children. Of the Nation's approximately 1,800 mental health clinics, somewhat less than one-fourth are child guidance clinics; moreover, only 32 percent of the 300,000 patients under 18 years seen at out-

patient clinics in 1963 were treated. A large proportion of all counties in the United States are without mental health clinics altogether, and most of these also lack agencies that substitute in some measure for such services.

Recognition of the terrible human and economic cost of the mental health problems of children led the Institute to establish the Center for Studies of Mental Health of Children and Youth. This Center will support the conduct of research, develop training programs for specialized manpower, and work toward the development of preventive programs and improved patterns for the delivery of services.

In order to prevent, control, and ameliorate emotional disorders in children, the Institute supports studies in genetics, biochemistry, neurophysiology, psychiatry, psychology, sociology, anthropology, epidemiology, and other disciplines. Many of these studies focus on specific psychopathological phenomena. But basic behavioral research—to obtain normative data on the physiological, psychological, and social growth of the normal child—is also an integral part of the Institute's program and in some respects the more important part. For the results of such research provide the baselines from which deviations in the development of the disturbed child can be measured and understood, and the insights by which many of the origins of adult illness can be identified. The Institute's basic research effort also reflects an important feature of the Institute's mission—its emphasis on mental health as well as illness, on work designed to enhance the child's potential—intellectual, emotional, social, cultural—as well as to resolve specific problems of psychopathology.

The Institute's work in child development focuses on three areas: the critical first years of life, the family, and the school. This concentration of effort reflects the fact that parents and teachers are the adults with whom the child spends the largest portion of his time and who are, then, in the main, the dominant influences on his life. To a large extent it is they, through the process of socializing and educating the child, who transmit the best—and the worst—of our culture from one generation to the next.

The work comprises a broad group of studies. Research on the family's contribution to a child's development extends from genetic influences at one end to the impact of social change on family life, and therefore on the child, at the other. Projects dealing with the school and the child include studies of learning, of school problems in deprived areas, and of the relationships between particular personality factors and learning and behavior. It will be seen that much of the research has implications either for improving our present services to children or for instituting new ones.

The campaign against child mental illness and for improved mental health among our youth is best fought and won in the child's natural environment. There are many children, however, who have been failed by these primary preventive resources and for whom special mental health services now become necessary. The latter represent a second line of defense, intended for the most part to help the troubled and troublesome child remain a functioning member of the community while being treated. The aim is to provide early help for the child suffering a mental or emotional disorder, thus forestalling more serious crises and institutionalization, and, hopefully, returning the child to a normal and productive life.

This range of services is broad. It includes treatment by pediatricians and general practitioners; treatment in general hospitals and at outpatient clinics; and a combination of treatment and education in special classes and special schools. Included also are the services of welfare agencies, whose workers are often the first to detect existing or impending emotional illness and to bring help to the afflicted person and his family. And, in the case of delinquent youngsters, the services encompass the work of court personnel, training school staffs, and probation officers.

Improvement of these services depends both upon advances in knowledge and upon demonstrations of how these advances can be applied.

The goals of prevention, early diagnosis and early treatment continue to guide the work of those in the child mental health field. But these goals are sometimes unattainable. Social and environmental conditions cannot be transformed overnight, the sick child is not always recognized early, treatment comes too late, or it is simply not effective. For such children—those whose problems become exacerbated, whose psychological suffering and social malfunctioning becomes intense—the concerted and intensive care offered in a residential setting is often the only answer. The aim here is to abort chronicity, to reverse the tide of psychopathology, to rehabilitate the child, and return him to normal life as soon as possible.

Efforts to meet the needs of children requiring residential care are being made by the Institute in a wide range of institutional settings; orphanages, foster homes, institutions for the mentally retarded, hospitals for the emotionally disturbed, and correctional institutions. All of these can be viewed as comprising a third line of defense in the struggle to overcome the forces, which research is identifying ever more closely, that make for mental illness, intellectual retardation, and antisocial behavior, and that prevent so many of us from realizing our capacities as human beings.

But these institutions, where we place children for a little or a long while because of some deviancy or misfortune—in their parents' lives if not their own—can compound the problem instead of easing it. The child raised in an orphanage may become crippled emotionally; the adolescent in a state mental hospital may drift into chronic mental illness; the youngster in a correctional institution may emerge more bitter against society than when he entered.

Consequently, the Institute supports a variety of research and demonstration projects to learn and show how institutional services can be improved—can be given a better chance of strengthening the emotional well-being of the children they serve.

A special program has been developed to study children's emotional illnesses. Section 231 of the Social Security Amendments of 1965 authorized the support of a comprehensive, national study and survey of the resources and methods for the prevention and treatment of emotional illness in children. In response to this legislation, the Joint Commission on Mental Health of Children, which was organized by leaders and national groups in the child mental health field, applied for and received a 2-year grant to carry out the provisions and intent of this section of the historic law. The Commission is composed of outstanding experts from such fields as child psychiatry, psychology, social work, law, medicine, pediatrics, welfare, and education. Representatives from related government agencies meet with the Board regularly and participate in relevant deliberations.

Currently, 28 national organizations with programs in the mental health field are affiliated with the Commission. Broadly, the Commission will study what is known and can be found out about children who are not thriving and adapting in the various areas of their lives; point to sectors for further research; recommend new approaches; devise more imaginative uses of existing measures to promote growth and change toward healthy productive development; delineate the social instruments through which movement of desired goals can be achieved. It is to be hoped that the Commission's final report will serve to focus attention on the problems of the mental health of children as the Annual Report of the Joint Commission on Mental Illness and Health did for the problem of adult mental illness.

In summary, then, progress has been made in this critically important area, but much remains to be done. New avenues of research must be opened, and older ones more fully explored; daring techniques for treating and rehabilitating the disturbed child must be developed, tested, and refined; increasingly large numbers of professionals must be trained and tuned to the mental health needs of our children—some dedicated to research, others to the delivery of services to others.

MENTAL HEALTH CAREER DEVELOPMENT

This program is designed to train mental health personnel for careers in the Public Health Service. At present, these programs are concentrating on the development of psychiatrists and mental health nurses. The selection procedures, rotational assignment patterns, and opportunities for advanced training and promotion are all designed to give the Service the highest qualified and motivated individuals to serve its mental health programs.

An increase of 12 positions and $957,000 will provide for additional staff, data processing, and other contractual services in support of the centers on narcotic and drug abuse, alcoholism, crime and delinquency, suicide prevention, and mental health in children and youth.

Included in the net increase is $11,000 for annualization of positions new in 1967, offset by non-recurring items and $4,000 for one less day of pay in 1968.

REGIONAL AND FIELD ACTIVITIES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	283	$2,354,000	321	$2,936,000	+38	+$582,000
Other expenses		2,294,000		4,652,000		+2,358,000
Total	283	4,648,000	321	7,588,000	+38	2,940,000

CENTER FOR EPIDEMIOLOGIC STUDIES

A Center has been established in order to develop a central focus for the support and conduct of epidemiologic studies and research. The program of this new center is designed to investigate and support investigations of the determinants of mental illness and health in populations, so as to gain new knowledge for improved public health methods of control and prevention.

The scarcity of professional personnel for epidemiologic work is nowhere more evident than in the mental health field. Explorations are going forward with expert consultants regarding ways and means of broadening the availability of manpower for the epidemiology programs in two fundamental directions: (1) develop postgraduate training centers where intensive training in epidemiology and the epidemiology of mental illness and health can be given in preparation for a research career in the field, and (2) stimulate, support and create new opportunities for research careers in which the trained epidemiologist can work, teach and advance professional epidemiology.

In 1968, it is planned to develop one or two postgraduate training centers for epidemiology, at universities or research centers where there is a strong and/or growing department of epidemiology, an active research interest in mental illness and health, and a good potential for attracting students from varied disciplines.

Studies of *major mental disorders* are being planned. Staff is preparing a comprehensive review of the present status of epidemiologic knowledge of *depression* and related states. It will review and analyze the relevant contributions of clinical, biological, psychological and sociocultural studies; consider conceptual issues relating to the characteristics, classification, etiology and sequelae of depression; and consider methodological issues concerning the feasibility of epidemiologic testing and appropriateness of study methods.

In *cooperative research*, staff is working in an Institute intramural pilot study being conducted in an isolated population of Mennonites by the Laboratory for Socio-environmental Studies. This is to lead to a longitudinal study which will attempt to find behavioral predisposing factors that may, through their influence on adjustment to environment, affect early mortality and subfertility. The Center for Studies of Mental Health of Children and Youth is also interested in this in order to develop ways of applying new research knowledge to program development.

Dramatic social changes are bringing into mental health focus new population groups which have not been studied by traditional mental health methods and which cannot be reached by traditional mental health services. It is pointing out the need for new types of mental health data and new data systems related to the design and delivery of services to these groups.

For this purpose, the traditional forms of medical epidemiology and the traditional social science methods are inadequate when used independently. Current mergers of these methods into new patterns seem to offer a more adequate inclusion of all of the significant variables involved.

Research programs in psychiatric epidemiology provide a major vehicle for supplementing clinical descriptions. Historical trends in incidence and prevalence and information about the environmental quality, location and distribution of cases of disorder, are aids in understanding the etiology of mental illness and in planning mental health service programs. In order to gain a comprehensive picture of the characteristics of disorders these data also need to be supplemented by the study of people who are suffering from a disorder but not receiving treatment, and by data describing risk populations in stressful environments. The traditional behavioral science research approach to studying mental health problems in the controlled setting of the laboratory, is being changed to include methods of participant conceptualization in the field.

MENTAL HEALTH STUDY CENTER

The Mental Health Study Center has functioned as a community research and experimental service operation to innovate new methods of service delivery, test their value, and also to provide a sound body of knowledge about the community, its characteristics, its organizations and social systems, and the relationship of these to mental health and mental illness.

As the national movement for provision of mental health care moves from a model based on separate resources to a comprehensive community mental health center model, so the Mental Health Study Center will develop a service program on this latter model to continue its demonstration and innovative role. The Center will serve as a demonstration model for community mental health practices, as a focus for the development of new methods of community collaboration, and as a training center in the principles of community psychiatry and community mental health. In this mission the Center will cooperate with other areas of the Institute and with other agencies in the community on questions of mutual interest and concern.

In addition the Center will serve as a focus for the study of problems and issues faced by centers across the country and as a place immediately available to the Institute for the examination and experimentation with new methods to foster continuing development in the field of mental health care. This will require a significant increase in the clinical operation and the assumption of a responsibility for a catchment area. The objective will be to apply the findings of various levels of research to the field of service to initiate and monitor new programs, and to foster new ways of community linkage and integration of the clinical services into the life of the community.

There remain many unsolved issues in community mental health and a great need to build up appropriate operational concepts for this new method of service operations and to delineate new roles and functions for professional groups operating in these new ways. The Center will give equal emphasis to service, demonstration, clinical and applied research, basic community research, and to the training of professional and subprofessional staff for new roles. The Center will test a variety of new and old hypotheses in community mental health and will examine the impact of programs both on individuals and on the communities from which they come.

Many centers across the country, while recognizing the need for research in this area, may not have the facilities for these activities; the Mental Health Study Center by emphasizing research can make a substantial and necessary contribution to the center movement in the Nation. Clinical studies and program evaluation will, therefore, be paralleled by community studies to look for social and social system factors that are concerned with the etiology, maintenance, and modification of emotional disturbance and illness.

REGIONAL STAFFS

The Institute staff in the DHEW Regional Offices, responsible for carrying out assistance to States, serve as Institute field units providing consultative and technical assistance to State and community agencies and institutions in implementing such programs as inservice training, hospital improvement projects, project grants, grants-in-aid, and construction and staffing of comprehensive community mental health centers. The ultimate goal of regional office operations, to maximize the utilization of resources provided to State and local agencies and institutions, is achieved through the development and implementation of Institute program activities to meet overall State needs at their current phase of development of mental health services.

In the current year the highest priority is being given to development of operating procedures to implement the new Comprehensive Community Mental Health Centers Program and to furnishing the States and communities with the initial and continuing consultation attendant with their participation in this new program. Program guidelines are being revised as necessary to best assist States in implementing their comprehensive mental health plans.

In 1968 high priority will be given to consultation and technical assistance to States and communities in the continuing development of Comprehensive Community Mental Health Centers, both construction and staffing. Special attention will also be given to the stimulation and development of programs in such areas as narcotic and drug abuse, prevention and control of alcoholism, child mental health, crime and delinquency, social problems, suicide prevention, and staff de-

velopment. Regional staffs will actively and systematically participate in the planning and coordination of Institute activities to insure maximum benefit to the States from the various Institute mechanisms of support and assistance.

NARCOTIC ADDICT REHABILITATION ACTIVITIES

With the passage of the "Narcotic Addict Rehabilitation Act of 1966" late in the last session of the Congress, the National government modified its approach to the problem of the treatment of the persons who come to it for treatment either as prisoner-patients or citizen-patients. A supplemenal appropriation to provide amounts necessary to implement this legislation during 1967 has been proposed. Besides changing the legal criteria for eligibility for treatment at the Federal level, the legislation also authorized activities which the Government could not carry out before. Foremost among these new authorities is the authority for the Surgeon General to provide supervised aftercare services (for those addicts in his custody) averaging 2½ years following their release from inpatient treatment. It has been lack of aftercare facilities, many professionals in this area believe, which has resulted in the high rate of recidivism among addicts released from institutional care.

With the new authorities contained in the recent legislation the following operational approach has been developed.

In keeping with community mental health concepts and to insure that close followup and supervision of the addicts will be maintained, contracts will be let with appropriate facilities near the homes of the addicts. To maintain an overview of the performance of the contracts and insure a high level of professional performance in aftercare and rehabilitation, it is planned to locate PHS personnel in the eleven metropolitan areas having the largest addict populations.

While these contracts will vary in size, it is estimated that it will cost approximately $11,640 per addict to provide aftercare, treatment and rehabilitation services during the approximately 2½ years he will be in the custody of the Surgeon General in the community.

It is anticipated that approximately 385 addicts will receive aftercare in the second half of 1968. An increase of 36 positions and $2,849,000 is requested for this purpose.

Also included is an increase of 2 positions and $95,000 for increased support of the Regional Offices in order to meet the growth in program responsibilities.

There is a reduction of $4,000 for one less day of pay in 1968 in this activity.

FORT WORTH AND LEXINGTON HOSPITALS

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	1,072	$7,591,000	1,072	$8,434,000	--------	+$843,000
Other expenses	--------	3,376,000	--------	2,106,000	--------	−1,270,000
Total	1,072	10,967,000	1,072	10,540,000	--------	−427,000

With the reorganization of the Public Health Service the Fort Worth and Lexington Hospitals have been transferred to the National Institute of Mental Health. Over the coming years the role of the Public Health Service in this area will be modified from one of primarily providing care to addicts to one of developing new knowledge and new methods of intervention, treatment, rehabilitation, and aftercare in the fields of drug abuse, drug dependence (addictive disorders) and specific personality disorders. At present there are almost no centers for clinical research in drug abuse and personality disorders in the United States. In keeping with these goals these two institutions have been redesignated as Clinical Research Centers.

The goals of clinical research will be to plan and carry out a broad program of studies on the management, treatment, rehabilitation, and aftercare of drug-dependent persons; as well as to plan and carry out a broad-range program of clinical and behavioral studies on the treatment, management, rehabilitation, and aftercare of persons with specific personality disorders. The facilities will serve as a model of treatment, training, and demonstration for professional and

other personnel concerned with treatment, rehabilitation, aftercare, and legal process problems related to personality disorders, drug dependence and abuse.

Drug abuse and other forms of antisocial behavior are viewed clinically as unsuccessful efforts of individuals with poor impulse control to cope with daily life. Though we do not yet fully understand all of the factors which underlie addiction and personality disorders, current treatment efforts seek ways to support the "weak" individual and to modify his environment in such a way that he will be able to develop better coping mechanisms as an alternative to deviant behavior. Available methods of rehabilitation are not generally effective. The majority of addicts and individuals manifesting symptomatic socially deviant behavior relapse after they are discharged from a hospital or prison. They have difficulty in becoming productive members of society and have little chance of succeeding if they return to the same setting where they were unsuccessful initially, particularly where no aftercare facilities are available.

NEED FOR RESEARCH

The waste of human lives through disability, the social misery, and the deleterious effect on the national economy make it imperative that intensive research be initated in numerous areas in which little or no investigation has as yet been undertaken. Many lists of possible research areas have been suggested. None of these can be exhaustive or complete. The clinical research effort will enable the Institute to increase the scope and depth of a concerted research effort in the fields of drug abuse and of the personality disorders in which it occurs. The insights gained from the study of other manifestations of personality disorders are required for a thorough understanding of personality mechanisms which produce such symptoms as drug abuse. Increased understanding of the dynamics of the drug abuser will, in turn, contribute to deeper understanding of personality disorders.

(*a*) At present the research activities at the hospitals are largely concerned with pharmacological and neurophysiological studies conducted by the Addiction Research Center, long a research arm of the Institute. The Fort Worth Hospital is conducting evaluative and follow-up studies with selected groups of patients from San Antonio and Houston in special projects. One of these is to test the effectiveness of providing a continuum of care for patients from San Antonio. The program will be shifted from traditional patterns of treatment to experimental and demonstration techniques. The results of these new approaches will be extensively evaluated and then field tested.

(*b*) Drug addiction is believed to be symptomatic of characterological disorders interrelated with social, cultural, and economic stress. The patient as he appears at the time of hospitalization is the product of these factors. Accordingly, future research must be more longitudinal, concentrating on the potential addict and the patient who has been discharged, rather than being limited to the physical and psychological symptoms of addiction *per se*.

(*c*) A major research challenge exists in the field of personality disorders as related to other socially deviant behavior. Little is known about the underlying dynamics of faulty personality development in general. Even less is known about the mechanisms underlying specific symptomatic manifestations of personality disorders that have a serious impact on society.

IMPACT OF THE NARCOTIC ADDICT REHABILITATION ACT

The Narcotic Addict Rehabilitation Act of 1966 (P.L. 89–793) has authorized the commitment for treatment and rehabilitation of narcotic addicts who come before Federal Courts in any of three different ways:

1. Those charged with a non-violent crime against the United States and committed to treatment in lieu of trial.
2. Those tried and convicted of a crime against the United States and sentenced to commitment for treatment.
3. Those not charged with any crime who are civilly committed for treatment.

Much of the responsibility for carrying out the provisions of this Act is vested in the Surgeon General with the balance of the responsibility being vested in the

Attorney General. When the Narcotic Addict Rehabilitation Act has been fully implemented it is projected that the patient population will be as follows:

Addicts admitted under NARA	1,104
Prisoner addicts admitted prior to NARA	350
Non-addict patients	400
Total patients	1,854

The necessity for clinical care activities at the clinical research centers in the early years of implementation of the Narcotic Addict Rehabilitation Act will delay conversion to a program of clinical research focusing on the problems of narcotic addiction, drug abuse and personality disorders. While the legislation provides for the examination and treatment in other facilities (Federal, state, local or private) the early effective date of the legislation precludes the early development of these kinds of contractual arrangements. Accordingly in early years of implementation of this legislation it will be necessary to continue to use the Fort Worth and Lexington facilities for the examination of alleged addicts and their institutional care.

Amounts necessary to implement this legislation in 1967 have been proposed as a supplemental appropriation in 1967.

There is a net decrease of $427,000 in this activity which includes a reduction of $353,000 in the programs under the Narcotic Addict Rehabilitation Act to be established in 1967. Also included is a reduction of $74,000 for nonrecurring equipment costs in the ongoing programs.

SCIENTIFIC COMMUNICATION AND PUBLIC EDUCATION

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	73	$1,000,000	73	$1,000,000		
Other expenses		640,000		1,640,000		+$1,000,000
Total	73	1,640,000	73	2,640,000		+1,000,000

The programs of the Institute are notable for their breadth; covering as they do most of the physical, social and behavioral sciences from chemistry anthropology to zoology; and the helping professions from organized religions through medicine, social work, nursing, and psychology to the police; as well as a wide range of lay publics from the well-informed layman to the student, to the person who has a family member afflicted with one of the mental disorders. This wide range of publics has served to broaden the base of national interest in the mental health field, and has created a series of continually increasing demands for information regarding developments not only in the Institute but across the total mental health field as well. Thus the Institute, as the focal point for mental health activity in the Public Health Service plays as important role in developing and improving communication, both within the scientific and professional disciplines represented in the mental health field and within the growing numbers and groups of citizens interested in mental health.

The Institute's activities in information, communications, and education comprise a broad spectrum and are focused principally: for scientific information through the National Clearinghouse for Mental Health Information, and for public education and information through the Public Information Branch.

NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

As the scientific and technical information center of the Institute, the National Clearinghouse for Mental Health Information has several broad objectives: (1) to establish and maintain a centralized resource for the systematic collection, storage, retrieval, and dissemination of information concerned with mental health; (2) to provide its users, both inside and outside the Institute, substantive information in response to inquiries and on regular distribution basis; (3) to compile, analyze, synthesize, and assess this mental health information in order that it may be effectively utilized in the achievement of the mental health program of the Institute.

Answering individual requests for information is one of the Clearinghouse's most important functions, and the number of requests has increased considerably in the past year. Inquiries covering all types of mental health information are now received from psychiatrists, psychologists, social workers, nurses, administrators, legislators, voluntary associations, students in the mental health field—indeed, from all the mental health community. The various kinds of questions range from those to which a simple straightforward, factual answer can be given to requests for information requiring complex, interpretative replies.

Distribution of information to large numbers of individuals is often accomplished most effectively and economically by publications. The clearinghouse, therefore, has compiled and disseminates a great deal of information through journals or single publications. These include the monthly *Psychopharmacology Abstracts*, quarterly *Mental Retardation Abstracts*, and bi-monthly *Crime* and *Delinquency Abstracts*. Three specialized newsletters—*Occupational Mental Health Notes*, *Drug Dependence and Abuse Notes*, and the *Psychopharmacology Bulletin*—are issued about every 4–8 weeks. The newsletters contain items on recent programmatic developments, summaries of meetings and conventions, citations to available abstracts or full abstracts, and announcements of interest to individuals working in these particular fields.

Bibliographies on the literature on Community Mental Health, Electroconvulsive Therapy, Electroencephalographic Studies Related to Mental Retardation and Hydrocephalus were published. In process and scheduled for early publication are an Annotated Guide to Mental Health Films; and Annotated Bibliography on Mental Health Education Pamphlets (including a section on effective use of such pamphlets); an Annotated Bibliography on Religion and Mental Health; a 3000-item bibliography on Drug Dependence and Abuse; a 2200-item bibliography on Recent Research on Schizophrenia and a Selective Annotated Bibliography on Suicide Prevention. Information on current research is also collected by the Clearinghouse, and in the areas of mental retardation and crime and delinquency, summaries of the projects appear in the abstract journal.

During 1966 several reviews and state-of-the-art papers were also prepared: "Occupational Mental Health: An Emerging Art," "Schizophrenia and Anti-Psychotic Drugs," "Counseling Parents of the Mentally Retarded," including an annotated bibliography, "Relations between Educational Programs for the Mentally Retarded and Culturally Deprived," "Instrumental Learning in Mental Retardates," and "Correctional Treatment in the Community."

The Clearinghouse is moving as rapidly as possible toward its goal of a fully operational mental health information service in 1968. Complete coverage of the published literature and the capability of answering inquiries based on all published reports should be achieved within the coming year. Expansion of the information base to include unpublished reports, research in progress, and other difficult-to-locate materials will proceed more slowly, but vigorous attempts will be made to have available all these kinds of information.

The integrated systems design will be tested and refined. More adequate computer design and programming is also under way. Abstract journals, newsletters, bibliographies, and reviews concerned with mental health of children, schizophrenia, alcoholism, suicide prevention, violence and other social problems, manpower and training, psychiatric nursing, and mental health services are all being planned; publications should be forthcoming during the next year.

PUBLIC EDUCATION AND INFORMATION

As the focal point for public information and education of the Institute, this branch activity plans and carries out services, programs, and projects to inform the media of public communication and the public concerning Institute research, training, and mental health services programs. As well, these include disseminating current knowledge and its application in the many-faceted problems of mental illness and mental health, on subject areas of critical interest to people from alcoholism and narcotics addiction and drug abuse, to suicide prevention and schizophrenia.

Thus, public education activities are extremely diversified and meet both program needs and public and professional interest. The following are examples of their range and diversity:

(1) Public inquiries (with some 16,000 received and handled during the year), press services and materials (numbering over 300 contacts with media and 200 press releases, articles, features, and other materials prepared and distributed as well as television and radio materials;

(2) motion picture films with productions such as a major film on community mental health centers and a new animated film short on community mental health centers;

(3) development and presentation of exhibits on the Institute's programs, with coverage of major association meetings in the mental health field during the year;

(4) publications, with 564,000 Institute educational booklets and leaflets distributed on various mental illness subjects and a new cartoon booklet titled "Hooked", dealing with drug addiction, released in recent months; achieving distribution of over one million copies in the current year.

In the coming year, it is anticipated that demands for services and materials will increase sharply. In the field of publications, new public education materials (including use of the "cartoon" booklet type) are in planning for the furtherance of programs for comprehensive mental health community centers, alcoholism, suicide prevention, narcotics and drug abuse, and other areas. Television and motion picture films and materials will occupy major attention; a series of short documentary films on mental health research accomplishments and on subject areas of great public interest such as delinquency and narcotics and drug abuse, is planned.

NARCOTIC AND DANGEROUS DRUG INFORMATION ABUSE

For many years it has been apparent that little information has been possesed by the public, and in fact by segments of the mental health professions, regarding narcotic and dangerous drugs. With the growing interest in these fields, it has become critically important that professionals and non-professionals alike, who are involved in programs related to drug addiction and abuse, be well informed concerning this important mental health area. It is planned to develop a scientific and public information program on narcotics and dangerous drugs directed toward all concerned fields and professions, such as education, the universities, medicine, public health, law, and judicial and enforcement agencies; and, importantly, community physicians, mental health workers, volunteer agencies, and the lay public.

An increase of $1,000,000 is requested for this purpose.

PROGRAM MANAGEMENT AND SERVICES

	1967 estimate		1968 estimate		Increase or decrease	
	Positions	Amount	Positions	Amount	Positions	Amount
Personnel compensation and benefits	323	$2,413,000	325	$2,421,000	+2	+$8,000
Other expenses		2,318,000		2,418,000		+100,000
Total	323	4,731,000	325	4,839,000	+2	+108,000

This activity includes the Immediate Office of the Director, the Offices of Program Planning and Evaluation, Program Liaison and Administrative Management.

IMMEDIATE OFFICE OF THE DIRECTOR

This office is responsible for planning, directing and administering the programs of the Institute.

OFFICE OF PROGRAM PLANNING AND EVALUATION

This office is responsible for development and coordination of the Institute's planning and program analysis activities. In addition it provides legislative reference services and advises on legislative matters in the field of mental health. Further it administers the biometrics programs of the Institute.

The biometrics research program continues to provide a basic core of statistical data required for the implementation and continued surveillance of various aspects of the Institute's program. To meet the increasing demands for data for new programs, plans are being formulated for the establishment of a systematic, current base of information on psychiatric facilities from which surveys can be carried out readily. This will include the collection, processing and analysis of basic statistical data describing such facilities as community mental

health centers, partial hospitalization facilities for the mentally ill and residential treatment centers for emotionally disturbed children, as well as similar activities now being carried out in relation to inpatient and outpatient facilities for the mentally ill. Psychiatric case registers are being used to coordinate and integrate data on the characteristics of patients coming under care in all mental health facilities within specific geographic areas. In addition to the use of registers for program planning and evaluation, increasing demands are being placed on them for studies and basic data related to some of the developing programs of the Institute, such as alcoholism, drug abuse and epidemiology. Metropolitan demographic and epidemiologic studies are being continued to assess the relationship of such socioeconomic factors as income, educational level and occupation to the probability of entering into psychiatric care in specific population groups. Studies are being planned to develop methods of estimating the need for psychiatric facilities within defined geographic areas. Such methods are much in demand by those developing comprehensive community mental health programs. Also in relation to these programs, major progress is being made in the development of a basic model for statistical analysis of the flow of patients through community mental health facilities. In the area of theoretical statistics and mathematics, research is being carried out on statistical problems in multivariate analysis and statistical inference, with particular emphasis on problems of multiple classification as applied to the classification of mental disorders, classification of symptoms and other attributes of ill individuals. Further studies are underway involving the application of mathematical techniques to research on biological processes affecting the brain.

OFFICE OF PROGRAM LIAISON

This office is responsible for coordinating Institute activities with DHEW components, other Federal agencies, international groups, and with regional, state, and local mental health agencies and citizen groups. It acts as the liaison between the Institute regional organization and other Institute program areas. As result of the reorganization it also performs grant application review and referral functions for the Institute.

OFFICE OF ADMINISTRATIVE MANAGEMENT

This office is responsible for centralized services in financial management, management policy, personnel management, grants and contracts management administrative services, and data processing activities. It has broad responsibility for the design, issuance, and implementation of administrative operating procedures for the conduct of Institute operations.

An increase of 2 positions and $112,000 will provide additional support necessary for these services.

Included in this net increase is $9,000 for annualization of positions new in 1967, offset by non-recurring items and $4,000 for one less day of pay in 1968.

Mental health research and services—New positions requested in 1968

	Grade	Annual salary
Planning, development, and administration of extramural research programs:		
Medical staff assistant	GS-15	$17,550
Clerical assistant	GS-6	5,867
Total (2)		23,417
Intramural research:		
Medical staff assistant	GS-13	12,873
Engineer	GS-12	10,927
Administrative staff assistant.	GS-9	7,696
Research technician	GS-7	6,451
Clerical assistant	GS-5	5,331
Animal caretaker	GS-4	4,776
Do	GS-3	4,269
Total (7)		52,323
Special mental health programs:		
Chief of branch (2)	GS-16	40,150
Public health program specialist.	GS-16	20,075
Public health program specialist (3).	GS-14	45,318
Medical staff assistant	GS-9	7,696
Clerical assistant (3)	GS-6	17,601
Clerical assistant (2)	GS-5	10,662
Total (12)		141,502
Regional and field activities:		
Chief of branch (1)	GS-17	$22,760
Medical officer (3)	GS-15	54,471
Administrative officer	GS-14	15,106
Medical staff assistant (2)	GS-14	30,212
Administrative officer	GS-13	12,873
Medical staff assistant (2)	GS-13	25,746
Administrative officer	GS-12	10,927
Medical staff assistant (5)	GS-12	54,635
Administrative officer (2)	GS-11	18,442
Medical staff assistant (1)	GS-11	9,221
Administrative assistant (3).	GS-9	23,088
Nurse (3)	GS-9	23,088
Clerical assistant (1)	GS-7	6,451
Clerical assistant (3)	GS-6	17,601
Clerical assistant (6)	GS-5	31,986
Clerical assistant (3)	GS-4	14,328
Total		370,935
Program management and services:		
Administrative officer (1)	GS-13	12,873
Clerical assistant (1)	GS-5	5,331
Total (2)		18,204
Total new positions, all activities (61).		606,381

Community Mental Health Resource Support

Amounts available for obligation

	1967	1968
Appropriation	$50, 000, 000	$100, 168, 000
Unobligated balance brought forward	43, 092, 000	
Comparative transfer from "Mental Health Research and Services"	32, 081, 000	
Total	125, 173, 000	100, 168, 000

Obligations by activity

	1967 estimate	1968 estimate	Increase or decrease
Grants for construction of community mental health centers	$93, 092, 000	$50, 000, 000	−$43, 092, 000
Grants for staffing of community mental health centers	32, 081, 000	46, 168, 000	+14, 087, 000
Construction and operationjof narcotic addict rehabilitation facilities		4, 000, 000	+4, 000, 000
Total obligations	125, 173, 000	100, 168, 000	−25, 005, 000

Obligations by object

	1967 estimate	1968 estimate	Increase or decrease
41 Grants, subsidies, and contributions (total obligations)	$125, 173, 000	$100, 168, 000	−$25, 005, 000

SUMMARY OF CHANGES

1967 enacted appropriation	$50, 000, 000
Unobligated balance brought forward	43, 092, 000
Comparative transfer from "Mental health research and services"	32, 081, 000
1967 total estimated obligations	125, 173, 000
1968 estimated obligations	100, 168, 000
Total change	−25, 005, 000

	Base		Changes from base	
	Positions	Amount	Positions	Amount
INCREASES				
1. Grants for staffing community mental health centers		$32, 081, 000		$14, 087, 000
2. Construction and operation of narcotic addict rehabilitation facilities				4, 000, 000
Total program increases		32, 081, 000		18, 087, 000
DECREASES				
1. Grants for construction of community mental health centers				−43, 092, 000
Total change requested				−25, 005, 000

EXPLANATION OF CHANGES

Grants for construction of community mental health centers.—New obligational authority is the same in 1967 and 1968; i.e., $50,000,000. Amounts available for obligation in 1967, however, include $43,092,000 appropriated in 1966 which remain available for obligation through June 30, 1967. These construction funds are available for a two-year period.

Grants for staffing of community mental health centers.—An increase of $14,087,000 will support 64 additional staffing grants.

Construction and operation of narcotic addict rehabilitation facilities.—An increase of $4,000,000 will provide for the construction and operations of narcotic addict rehabilitation facilities as authorized by the Narcotic Addict Rehabilitation Act of 1966 (Public Law 89–793).

AUTHORIZING LEGISLATURE FOR GRANTS

I. The following Sections of the Community Mental Health Centers Act, as amended, authorize grants under the subactivities "Grants for the construction of community mental health centers," and "Grants for staffing of community mental health centers."

Sec. 201. There are authorized to be appropriated, for grants for construction of public and other nonprofit community mental health centers, $35,000,000 for the fiscal year ending June 30, 1965, $50,000,000 for the fiscal year ending June 30, 1966, and $65,000,000 for the fiscal year ending June 30, 1967.

(New legislation for construction of community mental health centers is proposed for 1968).

Sec. 224. There are hereby authorized to be appropriated $19,500,000 for the fiscal year ending June 30, 1966, $24,000,000 for the fiscal year ending June 30, 1967, and $30,000,000 for the fiscal year ending June 30, 1968, to enable the Secretary to make initial grants to community mental health centers under the provisions of this part. For the fiscal year ending June 30, 1967, and each of the five succeeding years, there are hereby authorized to be appropriated such sums as may be necessary to make grants to such centers which have previously received a grant under this part and are eligible for such a grant for the year for which sums are being appropriated under this sentence.

II. The following Section of the Narcotic Addict Rehabilitation Act of 1966 authorizes grants under the subactivity "Construction and operations of narcotic addict rehabilitation facilities."

Sec. 402. (a)(2) to enter into jointly financed cooperative arrangements with State and local governments and public and private organizations and institutions with a view toward the developing, constructing, operating, staffing, and maintaining of treatment centers and facilities (including post-hospitalization treatment centers and facilities) for narcotic addicts within the States.

COMMUNITY MENTAL HEALTH RESOURCE SUPPORT

INTRODUCTION

The Community Mental Health Centers Program is the major national mental health program resource for stimulating, planning, and initiating State, local and individual action in the development of comprehensive mental health services in the communities of the nation. The grant programs provide support for the construction of new facilities or the expansion of existing ones, and for support, for an initial period, of professional and technical staff delivering new services.

Each Center program must assume responsibility for the mental health needs of the residents of a defined area; it must make its services readily accessible and available to all persons within that area; and it must assure continuity of care. The program is based upon scientific and professional knowledge that assures the effectiveness and feasibility of preventive treatment and rehabilitation programs in the community that promptly serve the individual and family in need; that prevent or decrease the need for costly long term hospitalization and custodial care; and that accent the dignity and human value of the individual, and family and community life.

Participation in the program requires careful planning at State, regional and local levels. This is necessary in order to provide a division of the State into mental health service areas; to assure planning for adequate services and allocation of resources to all areas, including both metropolitan and rural areas; and to assign priorities of need based on evaluation of problems and resources. As of June 30, 1966, forty-six States and Territories had accomplished approved State plans. By the end of 1967 it is expected that at least fifty-one States and Territories will have approved plans for participation in the program.

Through 1966 the obligation of $54,991,000 for both construction and staffing grants enabled initiation of 126 new community mental health centers in forty-four States and Territories. Both metropolitan and rural programs have been initiated. With each new community mental health center serving an average catchment area of 165,000 people, these centers will provide community services to areas with a total population of some 19 million persons. This year it is estimated that the $93,092,000 available for construction and the $32,081,000 available for staffing will enable initiating 147 new community mental health centers, for a total of 273 through 1967.

New inpatient services will be available in 40 percent of the centers funded, and in an additional 32 percent, they will be enlarged—either through new physical facilities, increased staff, or both.

Grants for construction of community mental health centers

Total grants for construction of community mental health centers:

1967 estimate	$93, 092, 000
1968 estimate	50, 000, 000
Increase or decrease	−43, 092, 000

All centers funded under the program must provide five essential services: inpatient service, emergency services, partial hospitalization, outpatient care, and consultation and education services; and support may be provided for additional services providing for a comprehensive program. Construction grants make provision for adequate physical facilities for these services, either facilities to house the entire program when none exist, or to expand existing facilities for new services that enable development of a center program.

The Community Mental Health Centers Act authorized appropriations for three years. $35,000,000 was appropriated in 1965, and $50,000,000 each in 1966 and 1967. Funds are allotted to the States on the basis of population and per capita income. In 1966, $39,561,000 of the funds available for 1965 and 1966 were obligated for construction assistance to 93 new community mental health centers. In 1967 the $93,092,000 available from 1966 and 1967 funds will enable construction assistance to 124 new centers, for a total of 217 new centers provided construction assistance since the beginning of the program.

The $50,000,000 requested for 1968 under a new authorization will enable construction assistance to 67 new centers, as well as for addition of some new services beyond the five essential services, to center programs previously initiated.

Over half of the centers currently under way will provide partial hospitalization facilities in areas where no such capacity existed before.

New outpatient services will be offered by 45 percent of the current centers, and an additional 40 percent plan to improve and expand existing therapeutic approaches used on an outpatient basis—including individual and group psychotherapy, family therapy, and drug treatment.

Half of the centers will offer new emergency services, and a third more will increase them beyond their present levels; many plan to publicize emergency facilities widely within the community in order to assure their increased use.

Forty percent of today's centers will offer new consultative services, and another 40 percent will broaden existing ones—reaching out to schools, churches, court and juvenile authorities, and welfare agencies.

The authorization for construction grants expires with 1967. In 1968 renewal of this program is being requested, at $50,000,000 for 1968. With the $46,168,000 requested for staffing grants, these funds will provide for continuation of 121 staffing grants and for initiation of an estimated 87 new community mental health centers, bringing the total to an estimated 372 centers since the beginning of the program.

In 1968 a new program of Federal assistance in the construction, operation, staffing and maintenance of facilities for the care and treatment of narcotic addicts is being initiated. Authorized by the "Narcotic Addict Rehabilitation Act

of 1966" this program will permit those States and localities with serious incidence of narcotic drug addiction to provide treatment facilities for addicts as part of their total mental health programming.

Allocations of grant-in-aid funds for construction of community mental health centers

State or territory	1966 allocations	1967 allocations	1968 allocations
Alabama	$1,136,491	$1,127,805	$1,113,037
Alaska	100,000	100,000	100,000
Arizona	415,843	426,116	429,924
Arkansas	656,991	661,194	632,076
California	3,965,461	4,043,559	4,100,530
Colorado	473,958	477,695	483,957
Connecticut	587,642	596,083	608,805
Delaware	103,149	103,608	110,015
District of Columbia	164,809	162,477	162,801
Florida	1,547,192	1,556,118	1,580,016
Georgia	1,312,334	1,310,055	1,294,765
Hawaii	174,096	172,364	168,144
Idaho	199,609	196,980	189,917
Illinois	2,331,996	2,349,631	2,345,728
Indiana	1,205,890	1,208,394	1,187,746
Iowa	721,746	708,080	695,349
Kansas	580,203	578,358	561,762
Kentucky	981,617	981,655	955,380
Louisiana	1,089,709	1,086,361	1,070,989
Maine	280,690	278,818	275,263
Maryland	794,840	806,745	832,930
Massachusetts	1,198,650	1,201,604	1,222,753
Michigan	2,006,571	1,957,368	1,950,412
Minnesota	909,273	912,550	896,403
Mississippi	875,372	869,459	836,126
Missouri	1,101,542	1,097,446	1,130,016
Montana	187,826	185,096	184,774
Nebraska	377,050	378,931	371,295
Nevada	100,000	100,000	100,000
New Hampshire	169,952	172,963	173,138
New Jersey	1,476,644	1,498,796	1,506,805
New Mexico	294,770	292,849	286,949
New York	3,886,577	3,891,318	3,958,354
North Carolina	1,498,962	1,491,856	1,501,811
North Dakota	185,030	177,357	183,825
Ohio	2,495,407	2,473,061	2,475,219
Oklahoma	706,069	703,186	685,810
Oregon	463,174	464,264	475,318
Pennsylvania	2,853,784	2,820,735	2,829,536
Rhode Island	225,920	220,947	215,636
South Carolina	855,851	851,383	846,963
South Dakota	201,356	200,875	199,056
Tennessee	1,187,117	1,190,569	1,181,004
Texas	2,872,257	2,888,542	2,918,627
Utah	265,912	268,282	268,471
Vermont	108,691	110,049	112,263
Virginia	1,227,109	1,215,884	1,207,721
Washington	723,793	714,321	700,992
West Virginia	546,353	539,860	543,135
Wisconsin	1,040,232	1,039,526	1,029,140
Wyoming	100,000	100,000	100,000
Guam	26,212	28,661	27,466
Puerto Rico	984,363	985,899	958,626
Virgin Islands	15,477	16,228	15,531
American Samoa	8,438	8,039	7,691
Total	50,000,000	50,000,000	50,000,000

Grants for staffing of community mental health centers

Total grants for staffing of community mental health centers:	
1967 estimate	$32,081,000
1968 estimate	46,168,000
Increase or decrease	+14,087,000

The staffing grants provide for initial support of professional and technical staff, enabling communities to establish basic community mental health services making use of local resources, and providing assistance while permanent sources of financial support are developed. Each grant is made for a period of 4 years and 3 months. For the first 15 months Federal funds may support 75

percent of eligible costs of staff for new services. During each of the three succeeding 12 month periods the matching rate declines to 60 percent, 45 percent, and 30 percent of eligible costs.

In 1966 awards were made for 54 new community mental health centers for a total obligation of $15,430,000. In 1967 it is expected that the $32,081,000 available will provide $19,170,000 for assistance to 67 new centers, and $12,911,000 for continuation grants for the 54 centers initiated in 1966. Thus, by the end of 1967 a total of 121 new centers will have received staffing grant assistance.

In 1968 it is anticipated that the $46,168,000 requested will provide $20,000,000 for new grants for 64 new centers, and for addition of some new services for centers initiated in 1966 and 1967. In addition, $26,168,000 will be required for continuation of the grants to the estimated 121 centers initiated in 1966 and 1967.

Distribution of grants for staffing of community mental health centers

	1967 estimate		1968 estimate		Increase or decrease	
	Number	Amount	Number	Amount	Number	Amount
1. Noncompeting continuations	54	$12,911,000	121	$26,168,000	+67	+$13,257,000
2. New	67	19,170,000	64	20,000,000	−3	+830,000
3. Total grants for staffing of community mental health centers	121	32,081,000	185	46,168,000	+64	+14,087,000

Construction and operation of narcotic addict rehabilitation facilities

Construction and operation of narcotic addict rehabilitation facilities:	
1967 estimate	0
1968 estimate	$4,000,000
Increase or decrease	+4,000,000

This program was authorized by the "Narcotic Addict Rehabilitation Act of 1966" (P.L. 89–793).

This amount provides for jointly financed cooperative arrangements with state and local governments and public and private institutions for the development, construction, operation, staffing and maintenace of treatment centers and facilities for narcotic addicts. Planning for these facilities will be consistent with the state plans for construction and staffing of community mental health centers.

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APPENDIX A

(Requested at page 477)

Reserves on Fiscal Year 1967 Appropriations

NIH's authority to obligate funds in fiscal year 1967 reflects, among other items which vary from the 1967 appropriation, a reserve of $7,552,000. This reserve consists of two general categories: (1) $1,975,000 restriction on the procurement of equipment, supplies, travel, printing; and (2) $5,577,000 restriction on the funding of research grants.

Both of these items represent NIH's participation in the 1967 anti-inflationary program. These savings were based on a set of principles which were applied to all of the Department's appropriations. The restrictions on procurement were percentage reductions applied across-the-board to all appropriations.

The restrictions on research grants were applied to each appropiation where the estimate of funds needed to finance future non-competing commitments was higher when the 1967 budget was formulated than a year later when the 1968 budget was developed. Grant estimates are prepared over a period of two years for each budget submission. Neither year is completed when the estimates are made. When the 1967 budget was submitted to the Congress, it contained estimates of our committed grant requirements for the fiscal year 1966, which was not yet ended and for fiscal year 1967. Similarly, the 1968 budget contained these estimates for 1967 and 1968. As stated above, the reserve assessed against our 1967 funds was taken on those appropriations where the first 1967 estimate was higher than the amount computed for 1967 non-competing commitments when the 1968 budget was developed.

This does not, however, mean that (1) the estimates are inaccurate; or (2) that the reserve can be absorbed without impact on the program. Neither impression is correct.

On an *over-all* NIH basis, there was only a difference of $224,000 between the 1967 estimate made for the 1967 budget and the 1967 estimate made for the 1968 budget. This constitutes less than one-tenth of 1 percent of our total 1967 continuation research grant funds of $281.7 million and, in fact, was an underestimate, not an overestimate, of our total needs.

There are, however, more significant variations when this estimate is broken down by each NIH appropriation, and in three instances—the Arthritis, Neurology and Child Health Institutes—overestimates were indicated. On the other hand, it should be noted that there were underestimates of need in two institutes, Cancer and Heart, and in four appropriations the estimates were so close as to be insignificant (Dental, Allergy, NIGMS, and the International Program).

There are two basic reasons why these reserves cannot be absorbed without some program curtailment. First, the Institutes which overestimated their commitments could have, as a consequence, funded more new, approved projects, whereas those which underestimated their commitments must necessarily divert funds they intended for new, approved projects to honor these commitments. Since the anti-inflationary program provides only for decreases where there were overestimates and not for increases where underestimates occurred, effect on the total grant program is considerably less money for funding new ideas which have been recommended for approval by the Advisory Councils.

Secondly, the estimates used to develop the 1968 budget request were made in the summer of 1966, and experience since then has already shown that several of the estimates for commitments are too low. Both the Arthritis and Child Health Institutes have requested release of the reserves to meet their total commitments.

NIH research grants, 1967 noncompeting continuations

Institute	1967 col. of 1967 President's budget	Computer estimate as of Dec. 12, 1967	Savings by Institute
Office of International Research	275	192	83
National Institute of General Medical Sciences	38,263	38,256	7
National Institute of Child Health and Human Development	25,192	23,494	1,698
National Cancer Institute	34,463	37,678	
National Heart Institute	61,306	63,507	
National Institute of Dental Research	7,394	7,455	
National Institute of Arthritis and Metabolic Diseases	53,550	52,144	1,406
National Institute of Allergy and Infectious Diseases	27,159	27,426	
National Institute of Neurological Diseases and Blindness	33,929	31,603	2,326
Environmental Health Sciences	2,917	2,860	57

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